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Consulting Engineers & Planners

OCCUPATIONAL EXPOSURE TO TRIMELLITIC ANHYDRIDE IN ONTARIO

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NOTE

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OCCUPATIONAL EXPOSURE TO TRIMELLITIC ANHYDRIDE IN ONTARIO

Prepared for the

Occupational Health and Safety Division
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GLOSSARY

ACGIH	American Conference of Governmental Industrial Hygienists
IMMUNOGLOBULIN	One of a family of closely related though not identical proteins which are capable of acting as antibodies. Five major types of immunoglobulins are normally present in the human adult: IgG (γG), with a molecular weight of 150,000; IgA (γA), with a molecular weight of approximately 150,000; IgM (μM), with a molecular weight of 900,000; IgD (γD), with unknown molecular weight; and IgE (γE) with a molecular weight of 190,000. Use of either system of naming the immunoglobulins is acceptable. ABBR: Ig.
IgA	The principal immunogobulin in exocrine secretions such as milk, respiratory and intestinal mucin, saliva and tears. This is probably important in protecting mucosal surfaces from invasion by pathogenic bacteria.
IgD	A rare myeloma protein which is present in normal human serum in very small amount.
IgE	A gamma globulin produced by cells of the lining of the respiratory and intestinal tract. IgE is important in forming reagin, q.v., antibodies.
IgG	The principal immunoglobulin in human serum. Because it moves across the placental barrier it is important in producing immunity in the infant prior to birth.
IgM	A globulin formed in almost every immune response during the early period of the reaction (all as defined by "Taber's Cyclopedic Medical Dictionary", 1981).

MSDS	Material Safety Data Sheet.
NIOSH	National Institute for Occupational Safety and Health (United States Department of Health and Human Services.
OSHA	Occupational Safety and Health Administration (US Department of Labour).
RTECS	Registry of Toxic Effects of Chemical Substances, published by National Institute for Occupational Safety and Health (United States).
STEC	The Short-Term Exposure Criteria are the maximum concentrations of agents in the air to which workers may be exposed from time to time. However, the exposure of workers to these maximum concentrations should be: a) for not more than 15 minutes b) not oftener than 4 times in a workday; and c) only after 60 minutes have elapsed from the time of the last previous exposure to such concentration*.
STEL	Short-term exposure limit, i.e. the maximal concentration to which workers can be exposed for a period up to 15 minutes continuously. Also "TLV®-STEL".
TLV®	"Threshold Limit Value" or airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. Three categories of Threshold Limit Value may be specified by ACGIH, TWA, STEL, or Ceiling.

* Definition from "Exposure Criteria for Potentially Harmful Agents and Substances in Workplaces", 1981, Ministry of Labour.

TWA	Time-weighted average concentration for a normal 8-hour workday or 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Also "TLV®-TWA".
TWAEC	The Time-Weighted Average Exposure Criteria are the time-weighted average concentrations or levels of an agent for a 40-hour week to which, it is believed, nearly all workers may be exposed day after day without experiencing adverse effects. The TWAEC are based on the 40-hour week to provide flexibility in maintaining workplace concentration or levels within the specified limits. The TWAEC are calculated by dividing the cumulative weekly exposure by 40, where the cumulative weekly exposure = $C_1T_1 + C_2T_2 \ldots + C_nT_n$ and T_1, $T_2 \ldots$, T_n are the times in hours which a worker is taken to be exposed to concentrations C_1, $C_2, \ldots, C_n$, respectively, during a workweek. Additionally, occupational exposure criteria for compounds having more than one isomer are for the sum of the concentrations of each of the isomers (e.g.: the sum of the concentrations of cis- and trans- acetylene dichloride or 1,2-dichlorethylene).*

* Definition from "Exposure Criteria for Potentially Harmful Agents and Substances in Workplaces", 1981, Ministry of Labour.

1. INTRODUCTION

This study was done for the Ontario Ministry of Labour, to gather background information on worker exposure to trimellitic anhydride (TMA) in Ontario industry. Trimellitic anhydride is a solid synthetic organic chemical, used in synthesis of vinyl plasticizers and coatings resins, and known to be capable of causing severe and potentially fatal respiratory disease.

The method used in the study was:

- a review of published material relating to health effects, analytical methods and exposure data;
- a questionnaire survey of Ontario users to determine exposure patterns, controls, costs and other relevant data;
- a survey of labour organizations and a relevant trade association;
- visits and interviews with TMA-using firms and workers;

The questionnaire used and a list of organizations to which it was sent, are shown in Appendix 1.

The study objectives were to complete and review information in five main areas:

- use and exposure
- control options
- health effects
- monitoring

- legislation
- options for regulatory control.

These companies using TMA supplied information via the questionnaires and subsequent discussions:

Ashland Chemicals, Mississauga*
BASF Canada, Cornwall
Benjamin Moore and Company Limited, Toronto
H.L. Blachford Limited, Mississauga
C.I.L. Inc., Willowdale*
Schenectady Chemicals Canada Ltd., Scarborough*
Sterling Limited, St. Catharines

Upon our request, we were permitted by three companies (asterisked) to make plant visits. All make water-dispersible resins although Schenectady Chemicals Canada Limited uses TMA primarily for wire enamels. Although permission to visit Ontario's only plasticizer manufacturer was sought, it was not forthcoming during the course of the study.

Questionnaires were sent and calls made to three labour organizations and one trade organization as well.

2. EXECUTIVE SUMMARY

Ontario industry has reported trimellitic anhydride (TMA) usage of about 200 tonnes in 1982. The sole North American manufacturer, Amoco, expects volume to increase sharply in 1983, by as much as 20%, and by an average rate of about 5% per year in following years.

Workers in industries using TMA are exposed primarily during loading operations for batch-produced plasticizers, wire enamel and water-dispersible resin production. The duration of each worker's exposure is very short, in the order of a few hours per year, but concentrations are high enough to cause acute eye and respiratory irritation.

A primary source of exposure several years ago was in the epoxy powder coating of pipes (using TMA in the epoxy formulation). This industry now reports use of TMA-free coatings only, so the potential for exposure to TMA no longer exists.

Approximately 100 workers in Ontario are potentially exposed to TMA. Most of these are exposed only briefly. Estimated exposure durations are from 1/4 hour to 40 hours/year.

Exposure to trimellitic anhydride dust or fume has resulted in respiratory illnesses, ranging from asthma-rhinitis and flu-like syndromes to severe and potentially fatal pulmonary disease. The first two appear to be the result of allergic sensitization; the cause of the latter is less clear and both immunologic and chemical toxicity mechanisms have been postulated.

TMA is also an acute irritant at high levels, affecting primarily the eyes and respiratory system.

TMA has not been found to be mutagenic in the Ames test, and no unequivocal data on carcinogenicity has been produced. Teratogenicity testing is being done in mid-1983. Results of testing for reproductive hazard have been negative.

There is one documented method for sampling TMA levels in air, a personal pump drawing air through a filter. Three methods of analysis are in use, based on gas and liquid chromatographic detection of derivatives of trimellitic anhydride. Good precision has been documented for each. Medical tests for TMA sensitization have been devised by researchers, but are not routinely available.

The exposure to TMA is primarily mitigated by local ventilation, material handling equipment, and personal protective equipment such as respiratory and eye protection. Substitution of other materials for TMA has been accomplished in the epoxy powder coating industry but does not appear practical elsewhere.

Economic impact of any controls on TMA will depend on the nature of the exposure limit set. Industry can meet the current Ontario exposure criteria if average exposures are averaged over eight hours.

However, for the hour or less at a time that TMA is handled, concentrations may be much higher, and control by engineering means may cause a serious economic burden. This burden is unlikely to be justified by the volume of the TMA- using product. Employment due solely to TMA-using product is small (though not identified specifically by respondents) since all TMA-using companies manufacture other products in very much greater volume. Impact on employment would not be expected to be great.

The majority of Ontario employers favoured a voluntary exposure limit. Infrequency of use was generally cited as a factor in determining the extent of controls. Responses from union and workers indicate that Ontario workers do not perceive TMA to be a major problem. If use were more prolonged, then personal protection - usually employed at present for TMA exposure mitigation - would be less acceptable.

Very few jurisdictions have specifically assigned exposure limits for TMA. Guidelines range from 0.039 to 0.05 mg/m^3 with widespread acceptance of the ACGIH value, 0.04 mg/m^3 for 8 hours of exposure. Saskatchewan and Alberta also have 15 minute exposure limits of 0.12 and 0.15 mg/m^3 respectively.

A major deficiency in TMA exposure data is the lack of information on the health effects of short-term exposures to elevated levels and the level at which the irritant effect occurs.

3. MANUFACTURING PROCESSES USING TRIMELLITIC ANHYDRIDE

3.1 Introduction

Trimellitic anhydride is a white crystalline solid, used in Ontario in the manufacture of plasticizers, water-dispersible polymers, and wire coatings. Its properties are shown in Table 1.

The sole manufacturer of trimellitic anhydride, Amoco Chemicals of Chicago, Illinois, has indicated a sales volume of some 300 to 400 tonnes/year in Ontario.(1) Aggregate figures obtained from Ontario industry for 1982 are less, about 200 tonnes. The source of this discrepancy has not been identified. Forecasts for 1983 are for increased use.

Historically, the major use in North America, including Ontario, has been in the manufacture of specialty plasticizers, for polyvinyl chloride. Examples of end products are automotive interior vinyl and electrical insulation. It is estimated by Amoco that over 80% of TMA sold in Ontario is used in such plasticizers.

Water-dispersible coating resins account for most of the rest of the TMA used. These resins are used as ingredients in water-based paint systems. Manufacture of wire coatings (to provide the high temperature resistance needed, for instance, in some motors), epoxies (as a curing agent) and specialties use under 5% each.

A significant increase in sales of TMA in Ontario is expected by Amoco in 1983, possibly by as much as 20% more than 1982. This is expected to be a short-term increase; longer term average is expected to be about 50% per year. This demand is fuelled by expected increases in demand for high temperature

insulation and automotive dashboards, which would in turn increase plasticizer use.(1) Long-term forecasts for Ontario alone have not been available, but Ontario usage is expected to parallel that in the overall North American market. Amoco's forecasted growth rates by use type are given below for years following 1983.

Plasticizers	-	5% increase per year
Dispersible Coatings	-	3% increase per year
Wire enamels	-	"small", circa 1% per year

Ontario epoxy manufacturers contacted uniformly report that they no longer use TMA in their coating systems, having reformulated in the interests of reduced work place hazard. However, Amoco indicates a continuing use of TMA as an epoxy curative in their overall markets.

All the industries that use TMA may be expected to have similar exposures among their material handling and warehouse staff. These workers would deal with TMA only in unloading it as it is delivered to the paint, transferring it to storage locations within the raw material storage area and taking it to the plant area where it is used. Because TMA is delivered in "tote bags" of 500 or 1000 kg, or in pallets of 1000 kg (44 bags) most such handling will be done using machinery such as lift trucks rather than by hand.

3.2 Plasticizer Manufacture

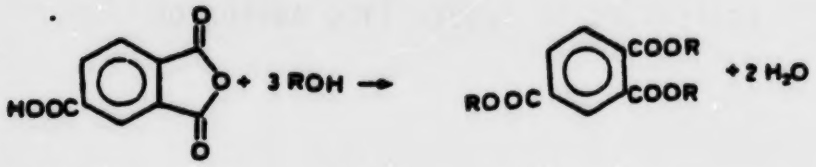
Plasticizers based on TMA are produced in batch processes by the esterification of a three-to-one molar ratio of monobasic alcohol (usually a C_7 - C_9 alcohol) to trimellitic anhydride. The sole Ontario producer, BASF, uses the C_8 alcohol 2-ethylhexanol (2-EHA), producing tri-2-ethylhexyl trimellitate. (TOTM)

TABLE 1
PROPERTIES OF TRIMELLITIC ANHYDRIDE

Synonyms

1,2-Anhydride; Anhydro Trimellic Acid; 1,2,4-Benzenetricarboxylic Acid; 1,2,4-Benzenetricarboxylic Acid Anhydride; 1,2,4-Benzenetricarboxylic acid; Cyclic 1,2-Anhydride; 1,2,4-Benzenetricarboxylic Anhydride; 4-Carboxyphthalic Anhydride; 1,3-Dihydro-1,3-Dioxo-5-Isobenzofurancarboxylic Acid; 1,3-Dioxo-5-Phthalancarboxylic Acid; 5-Phthalanacarboxylic Acid; 1,3-Dioxo; TMA; TMAN; Trimellic Acid Anhydride; Trimellic Acid 1,2-Anhydride, Trimellitic Acid Cyclic 1,2-Anhydride.(22)

		Reference
Formula	$C_9H_4O_5$	(16)
Molecular Weight	192.12	(60)
Melting Point °C	161 - 163.5	(60)
Boiling point (at 1.8 kPa), °C	240-245	(60)
Boiling point, °C	390	(16)
Flash point, °C (ASTM D-1310)	227	(16)
Density (water = 1)	1.54	(16)
Vapour Pressure (mmHg, 20°C) (kPa, 20°C)	$<7 \times 10^{-9}$ $<1 \times 10^{-9}$	(16)
Vapour Density (air = 1)	6.6	(16)
Odour	slight vinegar-like odour	(16)
Appearance	white flakes	(16)
Solubility, gm/100 gm solvent		
Water	hydrolyzes to acid, which is "moderately" soluble. Saturated solution has pH of 2	(16)
Carbon Tetrachloride	0.002	(60)
Mixed Xylenes	0.4	(60)
Acetone	49.6	(60)
CAS accession number	552-30-7	(22)
RTECS accession number	DC2050000	(22)



TMA 2-ethylhexanol Triester
R = C_8H_{17} (TOTM)

The reaction is carried out in a closed reactor or "kettle". Common sizes are 4500 to 13,000 L. The kettle is fitted with an agitator, a condenser-collector-system, loading piping for liquids, and loading ports, approximately manhole sized, for solids. It is equipped with external or internal heating and cooling systems and possibly an inert gas port to exclude air during reaction (air darkens the product).

The (liquid) alcohol portion of the charge is piped into the closed kettle and heated with agitation to a temperature below that required for reaction with TMA. A portion of the TMA (supplied in either 500 or 1000 kg "tote bags") is added through a hopper mounted over the (opened) loading port; the port is closed, heat is applied and the reaction commences. Note that the point at which exposure may occur is the discharging of TMA from the tote bag to the hopper.

Loading all of the TMA at once is impractical as a large part of the charge will then be solid, interferring with agitation and control of the reaction. Incremental addition avoids this problem.

As the reaction (esterification) proceeds, water is evolved in the form of steam, and is condensed and collected by a condenser-phase separator system. The batch is heated until the reaction, forming tri-2-ethylhexyl trimellitate, is

complete. At this stage no free TMA remains. A batch cycle may take 20 hours. A 10,000 L batch would use about 3,500 kg of TMA.

These compounds are valuable as plasticizers because of these advantageous properties:(2)

- they have good processability and compatibility in blending with polyvinyl chloride - mixing easily and remaining "compatible";
- they have good water resistance, like that of phthalate esters;
- they are low in volatility, like "polymeric" polyester plasticizers;

Properties are compared with those of some other plasticizers below:

TABLE 2

	Dibutyl Phthalate	Di-2-ethylhexyl Phthalate	Santicizer 409*	Tri-2-ethylhexyl Trimellitate	Plastolein 9720*	Di-2-ethylhexyl adipate
Viscosity, kPa.s	17	60	8000	255	430	11
Vapour pressure, kPa	12	0.2	-	N/A	N/A	0.3
Boiling Point, °C, at given pressure, kPa	340/101.3	231/0.7	-	260/0.1	N/A	214/0.7
Flash point, °C	340	425	564	505	564	385

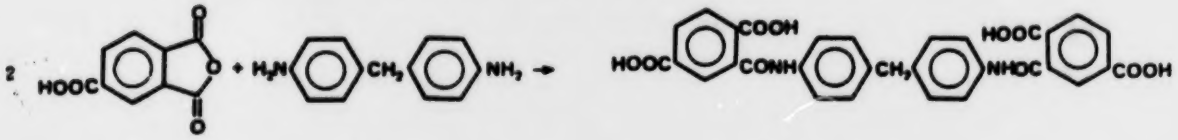
* Proprietary names for "polymeric" ester plasticizers.

The most commonly marketed trimellitate plasticizers are tri-2-ethylhexyl trimellitate and a triester of mixed heptyl and nonyl alcohols; these are said to be similar in overall properties.(3)

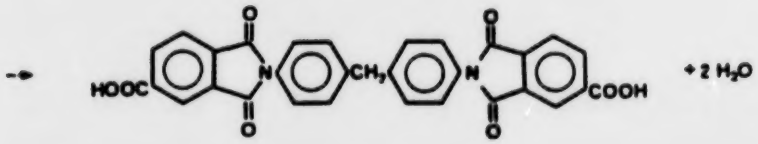
3.3 Wire Coating Manufacture

Polyimide-ester resins are produced in Ontario for use as heat resistant wire enamels by one company, Schenectady Chemicals Canada Limited. An aromatic diamine, methylene dianiline (MDA) for instance, is reacted with trimellitic anhydride in a 1:2 molar ratio; the anhydride-amine reaction forms an imide.(4) The imide group imparts desirable high temperature resistance to electrical insulation polymers.

The imide-forming reactions are:



TMA MDA I



II (Imide)

Trimellitic anhydride reacts with amines even at quite low temperatures to form an amide and acid(I). The rate of this

reaction is probably limited by solubility of the reactants and mobility of the product mixture. The conversion to the imide (II) is considered to begin at 150°C.(5)

The other, non-anhydridic acid group is reacted with polyols or diamines to form the polymer structure required to give good mechanical and coating properties as well as insulation and electrical properties.

The reaction is carried out in a batch process, in a closed reactor similar in principle to that used for plasticizers.

Since some reactants and reaction intermediates are solids at processing temperatures, the reaction is conducted in solvent to keep the batch fluid. The process consists of heating the reaction mixture, from an initial temperature below 150°C, to over 200°C, and distilling the water formed by the reactions.

The reactivity of the anhydride group ensures that no free TMA will remain in the mixture from quite an early stage of reaction. The stability of the imide linkage ensures that no TMA will be generated from the resin in its use application.

As with plasticizer manufacturing, loading of TMA to the reactor and material handling are the major exposure periods.

3.4 Water Dispersible Resins and Specialty Chemicals Manufacture

Water dispersible resins are made in Ontario for use in paint or priming applications. Such systems permit rapid and controlled application of coatings without the flammability

and toxicity associated with solvents. Questionnaire returns and comments from workers indicate that seven companies surveyed produce such resins. They are:

Ashland Chemicals
Benjamin Moore and Company Limited
H.L. Blachford Limited
C-I-L. Inc.
PPG Industries Canada Ltd.
Schenectady Chemicals Canada Ltd.
Sterling Limited.

The water dispersibility characteristic is imparted by incorporating into the resin polymer a number of uncombined organic acid residues. "Neutralizing" these with aqueous bases (such as ammonia) results in solution or dispersion of the resin in water. The resins may be "drying" resins, incorporating a fatty acid, or consist only of polyol and polyacid, depending on the use. The processing requirements are similar. In the following example, the processing of a drying resin is discussed.

Resins may be prepared according to the following general procedure.(6)

1. Excess polyol is combined with fatty acid and dibasic acid and reacted to a low residual uncombined acid content. This provides a hydroxy-terminated low molecular weight "prepolymer": a mixture of a glycol and its esters.

2. Trimellitic anhydride is then added to this prepolymer in a proportion that will leave 1/3 of its acid groups in excess. The mixture is reacted until esterification is complete. The reactors used in the production of

these resins are similar to those used for plasticizers and polyimide production. Reaction temperatures typically reach 180-195°C.

3. Water solubility or dispersibility is achieved by neutralizing with ammonia or amines. The resins are slowly added to a agitated "thinning tank" containing a water-alcohol-amine mixture and stirred until solution is complete. Examples of uses are "industrial baking primer" or "electrocoat".

Exposure potential is similar to that for plasticizer or wire coating manufacture.

3.5 Epoxy Curatives: "Powder Coating" or "Dry Coating"

Trimellitic anhydride has been used as a component in some epoxy resins, notably "powder coating" and some liquid coating systems. At the time of this study, no TMA-containing systems were reported by epoxy users, suppliers, or manufacturers surveyed. It is conceivable that such formulations may be used again. Note also that the TMA manufacturer, Amoco, says epoxy use is "holding its own", without describing specific use areas.

For information purposes, a short description of the relevant process formerly used by one Ontario epoxy coating producer is given below.

"Powder coating" refers to the application of a coating material to the substrate in the form of a fine powder, rather than in the traditional wet forms. Heating the object results in the powder in contact with it flowing to form a continuous smooth coat. Thermosetting coatings cure during

this process, becoming insoluble and infusible. Epoxy-based formulations are the largest volume thermosetting powder coat systems. These must include a curing agent in order to obtain the thermosetting effect. A variety of curing agents have been used, including trimellitic anhydride. As a curing agent, it is said to provide coatings with better performance in a number of areas; longevity and strength at high temperatures, elasticity, tensile strength, and improved electrical insulation properties. The latter makes them attractive in, for instance, circuit board work.

TMA is also attractive from a cost standpoint; competitive curing systems may cost $1.90/lb. while TMA costs $1.00/lb. at time of writing.

The manufacture of anhydride-cured epoxy powder coatings involves a number of processes. Basically, epoxy resin, TMA and other ingredients are charged to a blender, similar in principle to large household blender, where they are mixed. The mixture is conveyed (enclosed screw conveyor) to a (closed) extruder. The extruder melts the blend and extrudes it as a hot toothpaste-like ribbon. The ribbon is flattened between squeeze rollers, chilled on a cooling drum or belt, and chipped. From the chipper it is conveyed to an enclosed pulverizing mill where it is milled to powder. The powder is air-conveyed to a bag-house collector and then packaged in plastic bags for sale.(7)

Since this process is continuous, unlike those previously discussed, exposure may occur throughout the shift, though varying in different parts of the work place.

A common application of such compounds has been the coating of pipe for gas or oil pipelines, for corrosion protection. This is done by the following procedure:

Pipe, heated to 210-240°C, or still hot from previous processing, is conveyed past electrostatic powder spray guns enclosed in a spray booth. Powder is continuously sprayed at the moving pipe; it contacts the pipe, fuses and cures, generally within one minute. The pipe is conveyed away, sometimes through ovens to maintain it at curing temperature, and is then allowed to cool or is quenched with a water spray.

Factors affecting the cure include the substrate mass (a more massive pipe retains heat longer and gives an effectively longer cure time), the temperature, and the use of post-spray ovens.

Exposure to dust is continuous in this process. Exposure to fume is less widespread, but also continuous. Those working close to the pipe, such as inspectors, have been particularly vulnerable. Inspection of pipe to detect flaws in the coating is a critical part of the applicator's quality control. Continuity in the coating is very important as it can determine the corrosion resistance of the pipe.

Another possible use of TMA with epoxies (again, not produced in Ontario at present) is in the production of liquid coating systems. Here, the TMA is blended, heated or "prereacted" with a liquid epoxy resin in a heated tank, to produce a liquid system that will cure to a solid coating at higher temperatures. This type of resin is not used in the volumes that powder coats are; its uses are generally in electrical component work. It may be poured into moulds to encapsulate components; components may be dipped into a tank of the material, or less commonly, sprayed with it. The cure is affected by heating the mould or passing the dipped or sprayed part through a curing oven.(8)

4. EMISSIONS AND EXPOSURE

4.1 Introduction

The greatest exposures to TMA historically appear to have been in the epoxy-coating of pipe. However, due to industry-wide substitutions, this industry no longer uses TMA.

Other epoxy-coating operations would be likely to entail less exposure; small electrical components, for instance, use much less coating and the dust and fume evolution is correspondingly less. In any case, this is not practiced in Ontario at present.

Paint and wire coating resins and plasticizer production entail exposure only in loading and material handling.

It appears from the toxicology of TMA (discussed in Section 6) that products such as esters (plasticizers and resins) or imides (wire coatings) do not have the potential for the same toxic effects as TMA itself. Also, there has been no indication in the literature of TMA-related health effects in industries using products containing chemically combined TMA.

Consequently, discussion of exposure in this report will deal with the industries which use trimellitic anhydride itself, rather than those using products containing it in chemically combined forms.

An estimate of Ontario exposure in TMA-using industries based on questionnaire returns and interviews, is shown below.

TABLE 3

ESTIMATED WORKER EXPOSURE IN ONTARIO

Industry	No. of Companies	Total No. of Workers	Workers Potentially Exposed	Average Duration Exposure/Year
Water dispersible Paint & Coating Resins	6	837	92	1/4 hour to 4 hours
Wire enamel	1	51	27	<1 hour
Plasticizer	1	140	12	40 hours
Total	8	1028	131	

One firm did not supply an estimate for number of workers exposed. The number of workers exposed was estimated, from exposures in the industry.

The levels of trimellitic anhydride documented in this report have been extracted from the literature and obtained in discussions with Ontario industry representatives. While there are close similarities in the processes used by several companies, there are important detail differences between companies in use pattern and control technologies.

Literature values for average concentrations will reflect an eight hour exposure in epoxy coating industries and a fraction of an hour per batch in paint and related polymer operations. As might be expected, the duration of exposure has a major influence on the perception of the severity of the hazard.

4.2 Plasticizer Manufacture

Plasticizer manufacture accounts for most trimellitic anhydride consumption world-wide and in Ontario. Since trimellitic anhydride is a major component of plasticizers - about 1/3 of the charge - there is considerable container handling and unloading. The containers used in this application are 500 and 1000 kg cartons so that reactor charging does not necessitate manual lifting or bag handling. The number of workers in the loading area is also less than if manual handling were done. TMA dust released during loading of the reactor is the main source of worker exposure.

Other, incidental exposure will occur among warehouse workers in the event of container breakage or leakage.

In Ontario, the single plasticizer manufacturing facility using TMA, reported that worker exposure is as follows:

Operating crew	-	8 workers, during batch charging
Maintenance	-	2 workers, walk-through and during maintenance
Material Handling	-	2 workers handling cartons

This totals 5 to 10% of the workers in this industry.

These particular plasticizers are a minor component of the manufacturer's product line. Phthalate plasticizers, for instance, are sold in about 100 times greater volume(1), and this is reflected in the time spent in trimellitate processing.

Exposure to trimellitic anhydride is not continuous, occurring during the loading stage of the batch cycle. The estimated duration of potential exposure is under 10 hours per

month for three shifts of operating crews, or three hours/ month each. Maintenance and material handling exposures are less regular and would be expected to be shorter.

4.3 Dispersible Coatings and Specialty Chemicals

While dispersible coatings use much less trimellitic anhydride than plasticizers, seven companies have been identified as manufacturing them in Ontario. Of them, one also manufacturers polyimide wire coatings. Its practices are discussed separately, in Section 4.4. Characteristically, these firms make many other products and use trimellitic anhydride a few times a month to a few times per year.

The companies identified in our survey, as using TMA primarily in dispersible coatings and specialties, employed some 837 production workers, with an estimated 74 of these working with TMA in handling and loading of materials into reactors. Among them they produce some 30 to 50 batches of TMA-containing product annually. The duration of exposure during these loadings was estimated at from 10 minutes to 20 minutes per batch, with an average exposure time for operating crews in the individual companies of 1/4 hour to 4 hours per year for each worker.

The number of maintenance staff with the potential for occasional exposure is estimated at 18. These were estimated to be potentially exposed for from 1/2 hour to 1 hour per year. Walk-through exposure was not considered a probable occurrence by respondent companies; only one considered tha' a number about equal to the number of directly exposed workers might be exposed through dispersion through the plant to other, "Remote Departments".

In this industry, then, the number of directly exposed employees totals approximately 92. "Remote Department" worker exposure, during use or transfer of the TMA from storage to the reactor loading area, has not been included in the totals, as both the probability of exposure and its potential duration are very slight. Durations of exposure, even for those directly involved with TMA, are very low - typically under an hour per year average.

Exposure monitoring for TMA is not common in this industry. Only one firm reported an air sampling result; they had found a level of 0.04 mg/m^3 at the breathing zone of the worker who was loading TMA to the reactor. The sampling was done during and shortly after loading only, a period of about one hour.

4.4 Wire Enamel Manufacture

Ontario has only one wire-coating manufacturer using trimellitic anhydride. Exposure potential in this industry closely parallels that in the coatings industry. With 18 operating crew and nine maintenance and material handlers potentially exposed, the average annual exposure is of the order of an hour for the operating crews and less than that for others. There is very little opportunity for exposure of neighbouring workers.

Monitoring for exposure levels has not been done, but is expected by the author to be similar to that in the dispersible coatings industries.

4.5 Epoxy Manufacture and Use

No manufacturers of epoxy powder coatings in Ontario currently use TMA in their formulations. The major use of coatings containing TMA had, in the past, been the coating of pipe for oil and gas transmission. However, by about 1980, the industry had switched to non-TMA formulations, primarily for health and safety reasons.

Data on exposure is presented here for information purposes, and because the possibility may exist for manufacturing or use of TMA-containing formulations to occur in the future.

During the period when TMA was in use in epoxy powder coat systems, a manufacturer might use three crews of ten operators, helpers and material handlers, who would move around the production line and be exposed to dust or fume at different levels. Air samples taken on several occasions in an Ontario powder coat facility gave results ranging from less than 0.01 mg/m^3 to nearly 0.06 mg/m^3 TWA, compared with the ACGIH TLV® of 0.04 mg/m^3 and the Ontario proposed TWAEC of 0.039 mg/m^3. The total number of workers ever exposed under these conditions in Ontario was probably 30 to 50, and certainly less than 100.

Much of Canada's pipe coating has been done in Western Canada; firms coating pipe in Ontario have not used TMA-containing resin. The pipe coating plant of Shaw Industries Limited in Ontario had not begun operating before the move away from TMA had occurred.(7,9).

There is a potential use for TMA-epoxies in the electrical field. In Ontario, however, this survey has not indicated any such use, primarily because the relevant electrical components - circuit boards, for example - have been imported. Printed circuit board manufacture uses 40 x 10^6 lb of epoxy annually in the U.S. and none in Canada.(8) Future use is possible.

Some potential market exists both for the powder and for dip/encapsulation resins in specialty and "hand-built" applications, because of their advantageous properties. One distributor has indicated that he is actively attempting to market a TMA-cured powder system for such use, although none has been used so far in Ontario. Others have indicated that a small specialty section of the market is a logical target for materials with the properties conferred by a TMA cure.

On the whole, however, the consensus is that a few, not more than a dozen, manufacturers may be making or importing small quantities of TMA-epoxy coating and selling it a few gallons at a time where hand lamination is required. The potential for TMA exposure, even if maximum market penetration were to occur, would be among 40 to 50 end users, with an exposable work force of perhaps 200. In actuality, volume would be much less since market domination by TMA based resins is unlikely.

4.6 TMA Use and Exposure in Other Jurisdictions

Some data are available on exposure to TMA in the United States, but no documentation has been obtained from other sources. NIOSH, in Current Intelligence Bulletin No. 21(10) has estimated that 20,000 workers are at risk of exposure to TMA in the United States. Applications cited are:

- epoxy resin curative
- plasticizer manufacture
- paint and coatings
- polymer
- polyesters
- agricultural chemicals
- dyes and pigments

- pharmaceuticals
- surface active agents
- modifiers
- intermediates, and
- specialty chemicals

Measurements of TMA exposures were taken in some operations; these are tabulated below. From the reports these appear to be all time-weighted average area monitoring results, rather than personnel monitoring.

TABLE 4

	Nature of Business	Operation or Location	Range mg/m^3	Average mg/m^3	Ref
1.	Epoxy Manufacture (reported 1978) (U.S.)	Processing	ND to 4.0	1.5	(10)
		"Decontamination"	ND to 7.5	2.8	
2.	Pipe Coating (reported 1977) (U.S.)	Not stated (N/S)	0.11 to 0.27	N/S	(10)
3.	TMA Manufacture (reported 1976) (U.S.)	TMA condensation " drumming " bagging " warehouse		1.7 1.8 4.7 3.3	(11)
4.	Pipe Coating (reported 1979) (Alta.)	2 feet from booth*	N/S	0.27	(12)
		10 feet from booth*		0.1	
		40 feet from booth*		0.14	
5.	Electric Motor Components reported 1979 (U.S.)	Oven-curing powder coated parts	0.1 to 1.3	N/S	(13)

N/S = not stated, ND = none detected
* Distance from pipe not stated.

No newer data is available in the literature; however, considering the accelerating concern about TMA exposure since the late 1970's, it is expected that current control methods would tend to reduce these levels.

The U.S. exposed population, estimated at 20,000 may be contrasted with that of Ontario, previously estimated at 113 (above). The Ontario population is approximately 4% of that of the United States, suggesting an order of magnitude estimate of 0.04 x 20,000 = 800 Ontario workers at risk (in 1978, when NIOSH published its estimate). However, only a few of the applications cited by NIOSH are practiced in Ontario; plasticizers, paint and coatings resins, and wire coatings. Based on this smaller number of industry types - three, rather than the twelve cited by NIOSH - a reduced estimate, of the order of 200 potentially exposed workers, seems more realistic. Furthermore, NIOSH estimates included the high-risk, high-labour content, prolonged exposure conditions associated with epoxy formulation and application. These processes are no longer used in Ontario, and an estimate of either numbers or risk based on the epoxy-use premise is overstated.

4.7 Mixed Exposure

A complicating factor in assessing either exposure or the effects of exposure is the presence of other chemicals. In plasticizer manufacture, large volumes of alcohols, capable of irritation and longer term health effects, are used, as are other organic acids and diacids. The paint and resins industry often has solvents, acids, alcohols and polyols, styrene and phenols in the same general environment as TMA is used in, and possibly in the same product. Identifying a symptom as being characteristic of a particular chemical when several others are present is seldom straightforward.

5. EXPOSURE MITIGATION

5.1 Introduction

In general, exposure to TMA may be controlled in various ways, classifiable as:

- engineering controls
- product substitution
- administrative controls
- work practices or
- personal protective equipment

Engineering controls most commonly used are ventilation and segregation. Substitution of other materials is also practiced. Personal protection is generally used with, rather than as a substitute for, other controls.

Imposition of an exposure limit such as the TWAEC listed in the "Exposure Criteria for Potentially Harmful Agents and Substances in Workplaces" (14) would have little economic impact on Ontario industry. This is primarily because, at present, average exposure time is very low, and based on a 40-hour average exposure, most workplaces meet the TWAEC; engineering controls and protective equipment use are basically to protect against excursions.

Volume of TMA-based products is not a major factor in any sector of the Ontario economy, forming no more than a few percent of any user's production. Employment loss, were manufacturers unable to cope with an exposure limit, would be minimal as these products are not highly critical in determining the size of any company's work force.

Exposure to products containing chemically-combined TMA is not discussed (see Section 4.1).

5.2 Engineering Controls

5.2.1 Ventilation

In firms using TMA in Ontario, good general ventilation is normal because of the nature of other materials in the plant; organic acids, solvents, and alcohols for instance. Because TMA has a numerically low suggested limit compared to many more common industrial chemicals it is difficult to control exposure adequately by general ventilation alone. (The TLV® for TMA is 0.04 mg/m^3; for phthalic anhydride, 6 mg/m^3; for phenol, 19 mg/m^3; for xylene, 435 mg/m^3). This is recognized by firms using TMA. Local ventilation at the site where TMA is handled is common practice, providing reduction in TMA concentrations at the worker's breathing zone, and reducing dispersion of the material to other parts of the workplace.

This approach to ventilation has the advantage of providing a more effective air flow and dust scavenging than general ventilation, while being more cost effective. Considerably smaller volumes of air need be extracted than with general ventilation, so that less heated makeup air is needed. The ventilation may also be used only when and where needed - in this case, in small areas for short periods of time.

A local ventilation system may consist simply of a flexible 6 in. duct from an exhaust plenum with the intake mounted on the top of the loading funnel. Such systems were observed in visits to firms. (see Introduction)

5.2.2 Segregation

The structure of plants producing trimellitate derivatives in Ontario often aids in segregating the area where TMA is handled. One practice in the resin/polyester polymer industry in Ontario is for the building housing the reactor to have three floors. The top floor is used to load reactors, via chutes (for solids) to the reactor loading hatch on the second floor. The top floor then will contain raw materials in drums, bags, or cartons, and scales, pumps, and controls for metering liquids. It may also contain components of the ventilation system; drives, fans, and baghouse. The floor below is at the level of the top of the kettle and is an operating floor. It may contain liquid addition control and sampling systems, distillate controls, and the operator's batch recording station. The lowest floor, at the bottom of the reactor, has facilities for "unloading" the reactor - pumping, drumming, thinning and temporary storage. Plants with a two-floor plan combine the functions of the top two.

Materials present in quantity on one floor may not be in evidence at all on the others. This arrangement reduces the area of air contamination.

More restricted segregation of TMA handling is not widely practiced. Congestion around ports, intrusion of piping and process equipment and the need for handling large volumes of material (TMA and other raw materials) precludes enclosing the loading area in most instances.

5.2.3 Container Selection

Processes routinely using large quantities of TMA can reduce handling costs and exposure by using bulk containers, 500 to

1000 kg, instead of 22.6 kg bags. This, of course, requires a hopper loading system, with ancillary material handling and ventilation capacity. A bulk box, lifted with a fork lift or crane, may be opened and emptied into a hopper without worker presence at the hopper. If bags were used, the worker would manually handle 44 bags per tonne of TMA. Bulk containers are currently being used only in the plasticizer industry in Ontario. Other industries do not use sufficient quantities of TMA to justify bulk containers.

5.2.4 Bag Emptying

Observations in Ontario plants indicate that the normal practice in emptying bagged materials is to position the bag on the hopper, slash the bottom open with a knife, and shake once or twice. This requires the worker to closely approach the hopper throat, where dust is likely to be at its highest concentration. An alternative method demonstrated during plant visits is to use a hopper funnel equipped with crossbars with teeth. With this device the worker drops the bag end sharply onto the teeth, pulls to tear the bag, and shakes it. This system avoids approaching the throat as closely, and is used in some factories; others use the knife method, reasoning that most dust is ejected into the air by the shaking of the bag, and that more shaking is required with the toothed hopper method than the single slash method. Again, the preferred approach is probably a function of the hopper depth and height. This will be dictated by the loading station configuration - hopper flush with the floor or raised from the floor, angled or vertical - and the intrusion of other process equipment into the hopper area.

5.2.5 Fines Removal

While not currently applicable in Ontario, this may be a significant control method if epoxy-TMA-powder coatings are again used in Ontario.

In the processing of epoxy powder coat resins, the final step is grinding of the mixed epoxy-TMA-pigment blend to a powder of suitable size for coating, by spray or dip. However, the grinding process leaves some particles too large and reduces some to an unnecessarily fine size. Oversize particles interfere with the coating process, so they have been routinely removed; the fines, however, have not. A further separation stage, to remove these fines, has been implemented by at least one U.S. manufacturer.(15) This method has not been used in Ontario in the past but if a market is re-established for TMA-containing coatings it may be advantageous. The process would eliminate part of the dust hazard associated with spraying. It would not eliminate all of it, since more dust would be formed in material handling, and would not eliminate fume. Since fume problems are primarily associated with pipe, and pipe is not expected to be coated with TMA-resin, this could result in significant exposure reduction.

5.3 Use of Substitutes

This control method has been practiced primarily by the powder coat epoxy industry, to the extent that no Ontario manufacture or sale of TMA-containing epoxy is reported at present. Although substitution is apparently complete, it has not been an unqualified success - there have been trade-offs in quality and cost accompanying the changes, and some

industry members contacted have stated that none of the substitutes have provided properties as good as those of the TMA resins they replaced.(8) Substitutes are often amine-based although exact compositions are not generally stated.

Another type of substitution has been described in connection with epoxy use.(8) A curative consisting of TMA coated with a liquid (non-dusting) anhydride is being marketed, although not at present in Ontario. Use of such a curative would be expected to reduce TMA dust exposure in compounding and coating in comparison with TMA-only systems. It is expected that this would be a premium cost system, at least initially.

In the other industries using TMA in manufacturing, no reasonable substitute has been identified by any user.

5.4 Administrative Controls

The industries surveyed had very low annual exposure durations. Rotation of workers to equalize exposures has not been considered by any companies surveyed. However, most practice three shift operation so that the workers are to some extent effectively rotated.

5.5 Work Practices

Because TMA is dispersed primarily as dust, "housekeeping" has been emphasized strongly in industries using it. It is common practice, after loading TMA, to immediately cleanup and bundle bags for removal from the workplace and disposal.

This practice is not specific to TMA, but has historically been necessitated by the work environment, limited space and irritating dust and chemical residues in bags.

A practice that is specific to TMA is that of immediately immersing emptied bags into a drum of water, during loading. This eliminates dust in the handling and disposing of the bags. A small quantity of sodium hydroxide is added to the drum to neutralize the TMA. The drum is then sent for disposal. This procedure is not common among respondents and indeed would be practical only for processes using a very few bags at a time.

Although no workers claimed to have had skin irritation due to TMA exposure, one stated that workers made practice of showering as soon as possible after loading (bagged) TMA, even though a protective disposable coverall was worn.

Showering facilities are provided for workers by all companies surveyed; however showering is not specifically required by management for TMA workers. Double lockers were not provided by establishments observed.

5.6 Personal Protective Equipment

Personal protection is commonly directed to respiratory protection and skin and eye contact prevention.

5.6.1 Skin Contact

Precautions used for skin contact that have been cited are straightforward; use of gloves, face shields or goggles, and

aprons is quite common. Other firms require the use of disposable coveralls, and some have barrier cream available to be worn during TMA loading. Skin irritation was not highlighted as a problem, by workers; the reasoning behind coveralls and aprons is primarily to prevent contamination of clothing and subsequent inhalation of dust.

5.6.2 Eye Contact

In contrast to skin irritation, eye irritation was mentioned by workers as a common effect from TMA dust; the extent of the irritation, whether during loading or handling, or with or without eye protection, is less definite. Workers in the resin industry stated that eye irritation can occur when goggles or face shields are used.

It is common practice to require safety glasses or goggles in all plant areas in the industries surveyed, with supplementary protection such as face shields available. These devices are aimed at protection from splashes or impact, and not at dust protection. Considering the potential for eye irritation, masks affording full protection to the eyes - such as full face piece cartridge or supplied air respirators - are an obvious advantage, especially where exposure is to bursts of dusts released while emptying bags. Where both goggles and half-mask respirators are worn, interference between them can reduce eye protection.

Amoco recommends chemical goggles for protection (16); NIOSH recommends "dust resistant safety goggles".(10)

5.6.3 Respiratory Protection

Respiratory protection is commonly provided for protection against many chemicals in use in these industries. The types of respiratory protection devices stated by employers to be in use to protect workers from TMA are listed below:

- full face piece cartridge respirator
- double cartridge respirator
- Full face self-contained breathing apparatus
- Full face air supplied respirator
- Wilson R-21 (dual organic vapour cartridge half mask respirator)
- MSHA/NIOSH TC-21C-178 (organic vapour cartridge half mask respirator)
- 3M 8710 Dust/mist respirator half mask
- Scott organic vapour and dust mask
- half-mask respirator with high efficiency dust cartridge

All companies surveyed provide one or more mask types for use with TMA. Amoco recommends (16) a combination organic vapour/and gas/toxic particulate filter respirator, with a supplied air respirator to be used in (unspecified) "high concentrations". NIOSH (10) makes the following recommendations for various concentrations:

Where respirators are needed and NIOSH recommendations allow their use to reduce employee exposure, the following types of respirators may be used. They are listed in order of increasing protection factors.

- Protection factor of 50: any chemical cartridge respirator with a full face piece, organic vapor cartridge(s), and high efficiency filter(s) (30 CFR 11.150

and 11.30); any gas mask with a chin-style organic vapor canister and high efficiency filter (30 CFR 11.90(a) and 11.130); any supplied-air respirator with a full-face piece, helmet, or hood (30 CRF 11.110)(a); any self-contained breathing apparatus with a full face piece (30 CFR 11.70(a)).

- Protection factor of 1,000: any powdered air purifying chemical cartridge respirator with full face piece, organic vapor cartidges(s), and high efficiency particulate filter(s).

- Protection factor of 2,000: any type C supplied-air respirator with a full face piece operated in positive pressure-demand or other positive pressure mode or with a full face piece, hood, or helmet operated in continuous flow mode (30 CFR 11.110(a)).

- Protection factor of 10,000+: self-contained breathing apparatus with a full face piece operated in positive pressure-demand or other positive pressure mode (30 CFR 11.70(a)); any combination respirator which includes a type C supplied-air respirator with a full face piece operated in positive pressure-demand or other positive pressure or continuous flow mode and an auxillary self-contained breathing apparatus operated in positive pressure-demand or positive pressure mode (30 CFR 11.70(b)).

The use of full-face mask supplied air or SCBA is prevalent in firms that also have other low-exposure limit chemicals in their processes.

The drawback to their use is the restricted mobility that accompanies a bulkier and heavier mask especially in the case of SCBA or supplied air respirators. If a worker must remove his respiratory protection periodically to perform other job functions (such as bringing in materials, recording charges or observations in the log) much of the advantage of a superior protection factor is lost.

Epoxy-TMA powder coat safety data sheets, provided by the manufacturers, have recognized the TMA sensitization hazard. Recommendations include:

- local exhaust ventilation and full face chemical cartridge respirator with organic vapour cartidges and high efficiency filters;(17)

- a Protex 7511 respirator is given as an example by another manufacturer of a suitable respirator where ventilation is inadequate.(18)

5.7 Training

Training of workers in the hazards of TMA is typically included with general health and safety training by most companies. This is because TMA is considered one of many hazardous chemicals, and preparation for exposure to it is consistent with each company's overall health and safety program. Specific training for TMA includes, at minimum, familiarization with safety data sheets and handling precautions. The principles expressed in the general plant health

and safety training are otherwise assumed to apply. In one company, the approach is to classify chemicals according to hazard type, as follows:(19)

- dust
- skin irritant
- poison (including some dusts)
- fumes (vapour inhalation hazard)
- special (peroxides, explosives)
- extreme hazard (oxalic acid, TMA, maleic anhydride)

The last category, which includes TMA, has special handling instructions for each chemical. For TMA, a full-face supplied air respirator is required, along with immediate packaging cleanup and disposal of packaging materials.

5.8 Economic Impact of Controls

The industries using TMA in general also handle other chemicals requiring exposure controls, and because of this much of the mechanism for controlling TMA exposure is already in place. No company provided an estimate of the cost of controls, although some did give a value for total industrial hygiene and safety costs. Evidently the volume of TMA products alone has not justified engineering changes to any plant.

One report did indicate a system cost of $20,000 with an annual operating cost of $500 for local exhaust ventilation at the reactor. This system is however for general production use, not specifically for TMA.

The cost of handling TMA in bulk containers rather than bags was not addressed by those who had instituted that practice, and possibly it in fact reduced costs by reducing labour and handling. No company reported a TMA-specific medical program, and none, at time of writing, had established costs for monitoring of TMA.

Based on these statements, TMA-related incremental costs appear to involve only personal protective equipment. Total costs for personal protective equipment were estimated to range from about $7/per year to $200/year/employee; this included equipment for all employees and all chemicals, not specifically TMA.

Costs for medical examination programs, again for all employees and all hazards, were quoted as from $24 to $142/employee/year.

The low costs quoted for control are largely due to the sporadic nature of exposure. With only a few hours per year of TMA work, the time-weighted average exposure level will be very low, but characterized by excursions, probably above the TWAEC, for an hour or less at a time. All TMA users provide protection against these excursions and, realistically, an excursion limit is more suited to Ontario use patterns.

Because TMA products are a small part of each company's product line, and not vital to any company's existence, a more onerous standard would not pose a great threat to the companies. One spokesman indicated that if the costs of meeting the standard could not be met through product

pricing, the product would be dropped. Since there may be no production employment due solely to TMA products, changes in production will not have much effect on employment.

5.9 Worker Attitude to Controls

As well as manufacturing concerns, relevant labour organizations were contacted, to ascertain whether worker concerns and the need for government controls for TMA exposure were an issue. Comments from the labour organizations indicated that TMA has not been an issue. One union directed the study group to a worker exposed to TMA for comment.

Comments from TMA-workers pointed out that TMA was only one of many chemicals in the workplace, and that everyone in the workplace was accustomed to taking precautions with chemicals.

While emphasizing the use of safety data sheets and specialized handling for different chemicals, workers also pointed out that TMA was notably unpleasant to work with - causing discomfort to the eyes, nose and lungs when personal protection is not used. Operators and supervisors were familiar with the hazards indicated in the safety data sheets.

It is the conclusion of the authors that workers would probably favour engineering controls that would reduce exposure, if the controls did not interfere with their jobs. In discussions with workers, no suggestion as to the type of controls they might favour were forthcoming however. The

mandatory use of personal protective equipment for occasional short-term exposures is probably acceptable to workers, but continual use is less so, since the equipment restricts normal visibility, communications, mobility and comfort.

5.10 Employer Attitude to Controls

All employers contacted indicated that they recognized TMA as a serious problem worthy of every precaution. The response to this need has been, at minimum, to ensure that workers are informed of the hazard and to mandate the use of personal protection when TMA is handled. Monitoring is being done or planned by two companies, one in the resin industry, and one manufacturing plasticizers. There was no apparent difference in either attitude or awareness between large and small employers.

Concerning engineering controls, in general it is considered that TMA is used too irregularly to warrant a control system capable of lowering TMA levels to the order of the TLV®, even if it were available. Controls for TMA resemble those for other, similar hazards; specialized bag emptying, ventilation, and housekeeping. The plasticizer manufacturing firm, which uses much more TMA than the other companies, has begun using TMA in larger containers to minimize exposure.

6. HEALTH EFFECTS

6.1 Introduction

Inhalation of trimellitic anhydride has caused acute and/or chronic respiratory problems in some exposed workers. The most serious effect has been described as a pulmonary disease-anemia syndrome, characterized by coughing, hemoptysis, breathing difficulty, hypoxemia and anemia; the severity has ranged from mild to potentially fatal.(9) The mechanism of the disease is still the subject of research, with chemical pneumonitis and allergic sensitization being considered as possible contributory factors.

Two other effects of sensitization are more common - one characterized by asthma and rhinitis upon exposure, and the other by cough, wheezing and dyspnea and flu-like symptoms.

TMA causes coughing, rhinorrhea, nosebleed and breathing difficulty to workers exposed to high concentrations.

It can also cause severe eye burns. Skin irritation has been observed, but this is not considered a major hazard. Skin absorption has not been recorded.

Studies have indicated that the acute toxicity of TMA by ingestion is not high. It is not mutagenic in the Ames test. No studies on carcinogenicity have been completed. Completion of teratogenicity testing is planned for mid-1983 under the U.S National Toxicology Program.

6.2 Acute Toxicity

6.2.1 Ingestion

No human exposure by ingestion has been reported, but TMA has been tested in animal ingestion studies.(20) In 1958, a single-dose oral LD_{50} of 5-6 g/kg was found for rats; this was considered "practically non-toxic". Ninety-day feeding studies with dogs and rats were also conducted, starting in 1966. TMA concentrations at dietary levels up to 2% by weight were used, with no evidence of TMA-related health effects.

More recent testing (1979-1983) under the U.S. National Toxicology Program (NTP) has been inconclusive, primarily because of difficulty getting a sufficient dose into the test animal.(21) TMA is not sufficiently soluble in usual solvents to permit a large enough dose to be administered as a solution by gavage. The solvent finally used in the 1982 NTP test series was acetone; the solution was then mixed with trioctanoin. The maximum dose achievable was 1500 mg/kg. The test animal mortality at this and lower concentrations, using gavage, was insufficient to calculate an LD_{50}. The oral LD_{50} previously reported for mice is 2210 mg/kg.(22) The medium of administration was not specified.

Administering consistent large doses orally is complicated by the chemistry of TMA. It is sparingly soluble in non-toxic solvents and reacts with water to form trimellitic acid. As a result, any means of administration involving water as a diluent or suspending medium will invalidate the result since

the anhydride function of the TMA will be destroyed. Use of any solvent requires consideration of the toxicity of the solvent as well.

Toxicity of trimellitic acid and anhydride was discussed in 1970 by Batyrova et.al.(23) Results for trimellitic acid are summarized below:

Material	Species	Route	LD_{50} g/kg
Trimellitic Acid	Rat	intragastric	6.28
	Mouse		2.5
Trimellitic Acid	not stated	chronic dosing	3.157

Values for trimellitic anhydride were not given. The authors concluded that both compounds had irritating properties and that, although the anhydride was the stronger and more toxic of the two, both were only slightly toxic based on the LD_{50} results.

The toxicity data for trimellitic acid cited in RTECS(22) corresponds closely to that for TMA - an oral LD50 for mice of 2500 mg/kg, with a value of 1670 mg/kg for intra- peritoneal administration.

6.2.2 Contact

TMA is highly irritating to both eyes and skin.

Dermal LD_{50} values for rabbits of over 23 g/kg(21) indicate that TMA is relatively harmless when exposure is by this route. No observations of absorption have been reported.

Experience with eye irritation testing done in 1975, however, shows that TMA is corrosive to the eye when applied directly

to the eye as a powder. A mean eye irritation score of 105.6 out of 110.0 was obtained using the Draize test(24) in albino rabbits (see Appendix II). This indicates a highly destructive action on the eye. Earlier work indicated that TMA, applied to the eye as a 10% aqueous suspension, was "completely non-irritating".(28) This difference in effect may have been a result of partial hydrolysis of the TMA to the less-reactive trimellitic acid, when dispersed in water.(29)

6.2.3 Inhalation

Toxicity to humans by inhalation has been frequently reported.(11,12,25-36) There are several well characterized responses to inhalation of trimellitic anhydride reported, one of which is characterizable as acute toxicity (considered here to be the effect resulting from a single exposure). Trimellitic anhydride is a strong airway irritant. Typically, the irritant effect is characterized by cough and rhinorrhea, occasional nosebleed, difficult breathing and wheezing. Generally, it occurs after a "large exposure" to TMA fume or dust. There is no latent period between beginning employment in TMA work and response, and no apparent allergic sensitization. The symptoms recede over an eight- hour time span.

The effect is considered to be due to chemical irritation.(11,27,37,28,12,31,34,35,38)

The magnitude of the exposure needed to produce this effect is not documented. However, the irritation-based TLV for chemically-analogous phthalic anhydride is 6 mg/m^3, (14,11) suggesting that irritation is possible around that magnitude of concentration.

6.3 Chronic Toxicity

6.3.1 Allergic Sensitization

No reports are available documenting allergic sensitization following single acute exposures. The chronic effects of TMA inhalation have been the most severe and are the primary cause for concern regarding workplace exposure.

Workers subjected to repeated periods of exposure to trimellitic anhydride fumes or dust have shown symptoms consistent with allergic sensitization.(35) This has occurred in workers both with and without a history of allergies.(25) The symptoms are not produced on first exposure at work (unlike the case for acute exposure), but develop following a latent period. The workers so exposed then react to concentrations of TMA that do not elicit response in other exposed workers and to which they did not previously react themselves. This is in contrast to the irritant response, which follows a large exposure with no latent period.(11,12, 25-27, 29-31,39)

The studies on sensitization and its mechanisms have largely been done in the laboratories of Patterson and Zeiss of Northwestern University Medical School, Chicago, Illinois (11,28-30,33-36,38,39,41-45), supported by grants from Standard Oil Company of Indiana, National Institutes of Allergy and Infectious Diseases, Specialized Centre of Research, and the U.S. Public Health Service.

Three syndromes indicating possible sensitization have been discussed in the literature based on occupational exposure. The first, characterized by immediate-onset asthma and/or rhinitis, occurs some time after the first exposure, varying from a few weeks to several years.(11,27-29,31,32,34-36,39, 40,44). In affected workers, symptoms occur immediately upon

even momentary exposure and subside when the subject is withdrawn from (short-term) exposure. Some subjects were so sensitive that they could not tolerate being in the plant area even when not working at the TMA-related job.(29)

The second syndrome, described as "late respiratory systemic syndrome" (LRSS), consists of a cough, wheezing and dyspnea beginning after the work shift by four to eight hours.(11,27-29,32,34-36,39,40,44) Symptoms peak at night and are usually accompanied by "TMA flu" - chills, fever, aches in muscles and joints, and malaise. This response occurs after an induction period similar to that for the immediate onset asthma reaction. Sensitivity is similar. In reported cases workers have had to discontinue working on the TMA job.(29)

A third group of responses is described as pulmonary disease-anemia (PDA) syndrome.(12,20,26,29,30,32,34,36,39,44) It consists of cough, hemoptysis and dyspnea, reduced respiratory function, hypoxemia and anemia, with a period of at least a few weeks from first exposure to onset of symptoms. The severity has ranged from mild to potentially fatal, and one fatality possibly connected with it has been identified.(29) In this case, a patient who had intermittent TMA-fume exposure died of respiratory failure after pneumonitis of unknown cause. No autopsy was done; immunologic tests indicated, however, that TMA exposure had been sufficient to produce significant immunoresponse. Another subject had near-fatal respiratory failure.(29) While there is considerable evidence for an immunologic origin for the immediate onset and late respiratory systemic syndromes, the pulmonary disease-anemia syndrome has been considered both as a chemical pneumonitis effect and as an immunologic event. Possibly both may be involved.(46, 47) Fume, rather than dust exposure appears to be a key factor in this syndrome.

The symptoms and conditions of exposure resulting in disease are shown in Table 5, in chronological order as reported.

Because this table is compiled from the work of several authors, the emphasis on specific symptoms is not consistent, nor is the degree of interpretation that the authors put on the symptoms. It may be seen that author's viewpoints vary; each researcher's papers will reflect a particular interest. Some cases are described from an occupational health specialists' standpoint, for instance, and others from that of an immunologist.

It may be seen that reported illness is predominantly in the epoxy coating industry and in actual TMA manufacture. These industries have the most continuous exposure, and the only potential for TMA fume (rather than dust). The epoxy workers' illness often followed quite short induction periods, time spans in the order of a few weeks to a few months.

The effect of trimellitic anhydride upon tissue is considered to be due to reaction of the anhydride group with protein components. This type of reaction may potentially occur at a number of sites on a protein molecule, and Zeiss et al. have published work on the in-vitro synthesis of TMA - human serum albumin (HSA) conjugates which act as antigens.(11,28,29, 34-36,39-44, 48)(Appendix VII). The exact nature of the antigens is not described. However, analysis of conjugates synthesized in the laboratory indicates that reactive amine groups - presumed to be epsilon-amino groups of lysine - react under mild conditions (0°C), while more extensive reaction occurs at normal body temperature (37°C).(11)

TABLE 5
CHRONIC HEALTH EFFECTS OF TMA INHALATION

PROCESS	EXPOSURE CONDITIONS			EFFECT	COMMENTS	REFERENCE
	Concentration	Frequency	Induction Period			
Electrostatic epoxy spray pipe fittings 180°C	n/s	10 times/ year	1 year	Cough, breathlessness, wheezing for 24 hours	One patient; exposure conditions not given	(25) Faucett 1977
Epoxy spray pipe coating	n/s	daily	3 weeks	Dry cough, dyspnea, hemoptysis, bilateral pulmonary infiltrates ,"chemical pulmonary edema"	Inconsistent use of mask	(26) Rice 1977
	n/s	daily	6 weeks	Headache, cough, hemoptysis, dyspnea, fever, bilateral pulmonary infiltrates, "chemical pulmonary edema"	Mask usually used	(26)
TMA manufacture	1.7 to 4.7 mg/m^3	daily	2 weeks to 3-4 years	Three syndromes 1) rhinitis and asthma (6 workers) 2) late onset "TMA flu" (6 workers) 3) irritation on large exposure (acute effect) (6 workers)	13 worker retrospective study. Some workers exhibited more than one effect	(11) Zeiss 1977
Epoxy paint manufacture	1.5 mg/m^3 average, 7.5 mg/m^3 maximum	n/s	n/s	Eye and nasal irritation, shortness of breath, wheezing, cough, heartburn, nausea, headache, skin irritation, throat irritation	13 workers	(10) NIOSH 1978
Electrostatic epoxy spraying of cattle pens	n/s	daily	at least 1 month	Hemoptysis, shortness of breath, edema of nasal mucosa, blood from both upper lobe orifices	Irregular use of mask	(30) Ahmad 1979
			3 months	Hemoptysis, shortness of breath, wheezing, anemia	Irregular use of mask	(30) Ahmad 1979

n/s = not stated

TABLE 5

CHRONIC HEALTH EFFECTS OF TMA INHALATION

(continued)

PROCESS	EXPOSURE CONDITIONS			EFFECT	COMMENTS	REFERENCE
	Concentration	Frequency	Induction Period			
Electrostatic spraying of pipe	0.1 to 0.27 mg/m^3	daily	28-76 days	Cough, anterior chest discomfort, nose bleed, hemoptysis, dyspnea, fever, chills, weakness, vomiting, headache, hypoxemia, blood from segmental brochi	Retrospective study on seven hospitalized workers exposed to dust and fume	(12) Herbert 1979
Epoxy spraying of pipe	n/s	daily	6 weeks	Nearly fatal (1 worker) cough, malaise, weakness, anorexia, nausea, vomiting, hematemesis, melena, dyspnea, bilateral pulmonary infiltrates on X-ray, anemia		(33) Rivera 1981
Epoxy spraying of pipe	n/s	daily	3-8 weeks*	None (2 workers)	No information on ventilation or respirator use	(33) Rivera 1981
			2 weeks*	Rhinitis (1 worker)		
			2-7 months*	Cough, hemoptysis, dyspnea, myalgia or wheezing (3 workers)		
Oven curing epoxy powder-coated components	0.1 to 1.3 mg/m^3	n/s	n/s	Chest pain		(13) ACGIH 1981
Epoxy-TMA compounding	n/s	daily	at least 1-1/2 years*	Cough, myalgia (4 workers) shortness of breath, dyspnea, sneezing, tears (1 worker) cough, tightness (irritant) (2 workers) None (13 workers)	20 worker study: respirator use unknown	(34) Sale 1981

n/s = not stated

* = work exposure: induction period not stated

TABLE 5

CHRONIC HEALTH EFFECTS OF THA INHALATION

(concluded)

PROCESS	EXPOSURE CONDITIONS		EFFECT		COMMENTS	REFERENCE
	Concentration	Frequency	Induction Period			
Plasticizer manufacture	"High": not quantified.	daily	6-8 years*	Irritant (2 workers)	20 worker study by interview, questionnaire, and examination. Respirator use not stated.	(35) Bernstein 1982
			2 months to 9 years*	Asthma and/or rhinitis (3 workers)		
			8 years*	late respiratory systemic syndrome (1 worker)	Chemical mixers, operators and lab technician	
			1-10 years*	None (3 workers)		
	"Low": not quantified.	daily	10-20 years*	Irritant (5 workers)	Material handling, Supervisory and Technical staff	(36) Zeiss 1982
			18 years*	Late respiratory systemic syndrome (1 worker)		
				None (5 workers)		
THA manufacture	"Mild" to "high" dust or fumes	daily	"weeks to months".	Six workers developed asthma and/or rhinitis, five workers developed late respiratory systemic syndrome (cough, dyspnea, chills, etc.) and one showed both. 25 workers, including the above, developed antibody response; 36 did not.	61 worker study. Asthma and/or rhinitis was associated with mild dust fume exposure; late respiratory systemic syndrome with moderate dust or fumes, and pulmonary disease-anemia with high fume exposure. Irritant effects were associated with high dust or fume exposure. Antibody-positive workers had been exposed 1/2 to 8 years, antibody-negative workers, for 1-1/2 to 18 years.	

n/s = not stated

* = work exposure: induction period not stated

The quantitative composition of possible conjugates actually formed in the body has not been determined. Workplace variables will affect the concentrations of airborne TMA and, presumably the conjugate species produced.

Laboratory testing of workers with any of the three chronic response syndromes, using skin reaction and blood immunoreaction test techniques, showed antibody activity in response to lab-made TMA-protein conjugates. In addition, the testing could to some extent differentiate the workers with different syndromes, indicating that different immune-response mechanisms might exist for each.(11,29) There is a strong correlation of IgE antibody response with the rhinitis-asthma syndrome; total antibody activity with asthma and/or late-onset respiratory systemic syndrome; and IgA with respiratory syndromes. Correlation of IgM antibody and symptoms was not as clearly defined.(28)

Sensitivity to TMA is reported to diminish after workers are removed from TMA exposure (for example, after a few years).(34) This implies a process of removal or neutralization of the TMA-protein complex; however, studies on the degradation pathways have not been reported.

Other workers have also studied TMA toxicity.(25,26,12) Bronchial asthma associated with exposure to epoxy resin systems has been investigated by inhalation challenge testing by Fawcett et al.(25) Positive results were obtained for various curing systems - TMA, phthalic anhydride (PA), and triethylene tetramine. It was noted that response is specific to each chemical; exposure and sensitization to phthalic anhydride did not result in sensitivity to trimellitic anhydride.

Rice et al.(26) have discussed the cases of two workers who developed chemical pneumonitis following exposure to TMA-cured epoxy pipe coating. They considered the possibility of a hypersensitivity reaction causing this response, but observed that open lung biopsy showed changes consistent with a non- specific irritant effect capable of causing diffuse lung injury.

Herbert and Orford (12) also discussed extensive clinical testing and observation of patients with acute pulmonary hemorrhage, edema and anemia following TMA-epoxy pipe coating exposures. They stated that the most likely mechanism was a direct toxic effect on the alveolar tissues rather than an immunologic event. This study showed no workers developing asthma or allergic rhinitis after employment, and no "TMA flu". The authors conclude that the mechanism of the respiratory component may be nonimmunologic and that of the hematologic abnormalities could not be determined from their data.

In summary, the asthma-rhinitis syndrome and late respiratory systemic syndrome appear to be immune-mediated, while the case for the pulmonary disease syndrome, associated primarily with pipe coating, is less certain. There are observations consistent with either an immunologic mechanism or direct toxic effects causing the latter.

It is notable that this syndrome has been associated only with operations such as pipe coating that evolve TMA fume.

6.3.2 Carcinogenicity

In 1979, carcinogenicity testing of TMA was scheduled by the National Cancer Institute, now under the National

Toxicological Program. At this time no report of carcinogenicity has been published.(21,49,50) According to NTP no adequate data on carcinogenicity has been produced due to methodological problems with the testing. The most realistic route for exposure testing is by inhalation, but no method for quantifying exposure to the low levels needed for such a test is available to the NTP. They are currently considering this question with Amoco, the manufacturer of TMA, who are developing a low level dust/fume generator capable of producing consistent low levels of exposure.

Oral exposure (in food) has also been a problem - not enough TMA can be dissolved in carrier vehicle to produce a demonstrable effect. This has hampered both chronic and acute toxicity studies.

6.3.3 Mutagenicity

Trimellitic anhydride was tested for mutagenicity in 1982 under the United States National Toxicology Program(49. The salmonella typhimurium test (Ames test) is used in this program, at five doses, in triplicate, in each of four salmonella strains (TA-98,TA-100,TA-1535, and TA-1537). Results were negative. As only chemicals showing a positive or equivocal response are further tested, NTP does not plan additional mutagenicity testing on TMA.(21)

6.3.4 Teratogenicity

Trimellitic anhydride has been selected for testing by the National Centre for Toxicological Research (NCTR) and NIOSH. It is currently scheduled for re-test in a few months: the

original test results were inconclusive, apparently due to insufficient dose (based on the survival rate of the test animals to which it was administered).(21)

6.3.5 Reproductive Hazard

The post-natal mouse screening test of Chernoff and Kavlock(51) has predicted no reproductive hazard from TMA.

The test method, briefly, involves administering the test substance dispersed in corn oil, by gavage to pregnant mice, and comparing the offspring to a control group. Signs of toxicity as well as litter size, weight, and viability are noted. The dose applied to each dam is the highest dose which resulted in a small number of mortalities and/or significant weight loss, previously determined.

7. MONITORING

7.1 Introduction

Prior to the development of the NIOSH method of analyzing for trimellitic anhydride, no techniques specific to it had met NIOSH qualification criteria (52) (see Appendix I-II). The NIOSH method (53) (see Appendix IV) was developed to provide a standard of analysis, and preferably one which is simple, rapid, and quantitative.

The method selected is applicable to samples for both respirable and total particulate trimellitic anhydride. A one-step sample treatment converts trimellitic anhydride to trimethyl trimellitate. The trimethyl trimellitate is then measured quantitatively by gas chromatograph. No interferences by other substances have been cited.

In an alternate method (Appendix V) developed in the U.K. by the Health and Safety Executive, trimellitic anhydride is hydrolyzed to the sodium salt, and the salt is analyzed by liquid chromatography. Again, interferences from epoxy and phthalic anhydride were not observed.

The manufacturer of TMA, Amoco Chemicals, analyzes TMA extracted from a sample filter with an acetonitrile-water solution by liquid chromatography, using acetonitrile-water as the mobile phase (55) (see Appendix VI).

None of these methods distinguishes trimellitic <u>acid</u> from trimellitic <u>anhydride</u>. However, for occupational exposure purposes this is unlikely to be a significant problem. This is discussed in Appendix V.

7.2 NIOSH Recommendation

The NIOSH recommended method (53) for sampling and analysis is shown in Appendix IV.

The air sampling techniques used for trimellitic anhydride are straightforward and require no unusual precautions. TMA particulates are collected on a cassette-mounted PVC copolymer membrane filter; air flow is provided by a personal sampling pump operating at 1.7 L/min. The same method is adaptable for both total and respirable particulates, and it may be used for either area or personal monitoring. The NIOSH analytical method is calibrated for 19.2 to 96 μg trimellitic anhydride, so the sample time must be selected with these quantities in mind. For instance, 19.2 μg would be collected from air contaminated at the 0.04 mg/m^3 level in about five hours; 96 μg would take 25 hours. If lower levels, below the TLV®, are present, sample quantities will fall outside the calibration range.

Sample analysis is by gas-liquid chromatographic (GLC) analysis of trimethyl trimellitate, prepared by esterifying the trimellitic anhydride sample. The sample size for which the method is calibrated is much greater than is needed for high performance liquid chromatography (HPLC); the Amoco (HPLC) method is said to be sensitive down to 1 μg. Consequently, precision at very low concentrations is not as good as it is for HPLC and where low concentrations are expected the method may be unsatisfactory. However, gas chromatography is more widely used than HPLC and this method permits use of this instrument type.

The NIOSH method quotes a relative standard deviation for their calibration standard range (21 samples) of 7.6%.

There are some precautions necessary to obtain good results, however,

- the method calls for Teflon-lined screw caps for the derivatization tubes. Teflon is necessary because plasticizers in other liners will leak into the reaction mixture, possibly causing erroneous results if their elution times are near that of trimethyl trimellitate;

- because the solvents evaporate rapidly, the analyst must minimize the open time of the derivatization tubes while adding reagents and solvents.

- the flame ionization detector collector ring must be cleaned periodically with methanol to maintain sensitivity.

There are few problems with interference from other substances. Chromatograph temperature is sufficiently high that common volatile contaminants elute with the solvent fraction. The dimethyl ester of phthalic anhydride, a possible component of anhydride-contaminated atmospheres, elutes significantly earlier than trimethyl trimellitate and does not interfere with the analysis; dimethyl maleate and succinate elute with the solvents, and do not effect TMA analyses.

7.3 Health and Safety Executive Method

This method (54), developed by the Health and Safety Executive, Occupational Medicine and Hygiene Laboratories, in the U.K., is described in Appendix V.

This method as described does not discriminate between total particulate and respirable trimellitic anhydride. However, use of a cyclonic separator to obtain respirable-size-only particles does not appear to be precluded.

The sample is collected by passing an air volume of approximately 100 L through a GF/A filter in a Gelman holder at 2 L/minute. No special handling or storage precautions were noted. The samples are washed from the filters with sodium hydroxide solution and analyzed by HPLC.

The calibration of the method was done with sample quantities from 1.3 to 16 µg. This is considerably less than is required by the NIOSH method (19.2 to 96 µg calibration range). Consequently, the method is useful with shorter sample periods or lower airborne concentrations. Using the method as given, it is calibrated for air concentrations of 0.013 to 0.16 mg/m^3, a range conveniently close to recommended exposure limits (0.039 to 0.05 mg/m^3). This corresponds to a sample time under an hour at expected concentrations, so that sampling time is conveniently short and sampling may be done satisfactorily during, for instance, reactor charging.

Over the calibration range used (24 samples) a coefficient of variation for the analysis of 5.8% is quoted.

7.4 Amoco Method

Trimellitic anhydride is collected by an air pump and filter sampling system. The collected sample is washed from the filter with a solution of acetonitrile in water, and allowed to hydrolyze to trimellitic acid. This is then quantitated by HPLC.

The method has the advantage of a simpler solvent system than that used in the method of the Health and Safety Executive.

The calibration range, based on a 5 to 25 µg sample, corresponds to a one to four hour sample time at the TLV®; however, the method is adaptable to higher or lower concentrations and would be suitable for samples taken in typical loading situations, where exposure is about an hour.

The reproducibility cited for the analysis is quite consistent, the analytical procedure citing a relative standard deviation of ± 2.9% over 5 determinations. Interferences by other materials have not been discussed.

A difficulty with monitoring exists in that the amount of sample required may take an unreasonable length of time to collect with an air pump that delivers about 1.7 L/minute. The sampling durations necessary to obtain samples suitable for each of these methods, from air containing various levels of TMA, are shown below.

TABLE 6

	NIOSH	Health and Safety Executive	Amoco
Minimum sample quantity the method is calibrated for, µg	19.2	1.3	5
Maximum sample quantity the method is calibrated for, µg	96	16	25
Sampling time required to collect minimum quantity from air containing 0.04 mg/m^3 (TLV®)	4.7 hr.	20 min.	1.2 hr.
Sampling time required to collect maximum quantity from air containing 0.04 mg/m^3	23.5 hr.	4.1 hr.	6 hr.
Sampling time required for minimum quantity from air containing 0.15 mg/m^3 (Alberta 15 minute limit)	1.3 hr.	6 min.	20 min.
Sampling time required for maximum quantity from air containing 0.15 mg/m3	6.5 hr.	1.25 hr.	1.7 hr.

7.5 Medical Monitoring

While no method of measuring TMA residues in the body has been used, Zeiss et al. (11) have described methods for synthesizing TMA human serum albumin conjugates (Appendix VII). Using this synthetic antigen, they have measured antibodies reacting to it in exposed workers' blood samples. Workers with the asthma-rhinitis syndrome developed IgE antibody specific to TMA conjugates; IgG antibody specific to TMA conjugate was found in workers with the TMA-flu sydrome. Research is continuing on characterization of possible immune mechanisms or correlations for the "PDA" syndrome.

The test procedures at this time are used as research tools rather than as a standard diagnostic procedure.

8. CONTROL IN OTHER JURISDICTIONS

8.1 Introduction

Exposure limits for trimellitic anhydride have generally been promulgated only recently, since the late 1970s. .

In Canada, Alberta and Saskatchewan have introduced both 8 hour and 15 minutes workplace exposure limits for TMA in their lists of exposure limits. Ontario includes a 40-hour Time Weighted Average Exposure Criteria of 0.039 mg/m^3 for TMA in "Exposure Criteria for Potentially Harmful Agents and Substances in Workplaces. (for discussion only)". Generally, Canada and the United States rely largely on guidelines recommended by the American Conference of Governmental Industrial Hygienists (ACGIH).(57) European limits are also similar to those of ACGIH.

8.2 Canada

The federal government and provinces share the legislative authority in employment health and safety matters in Canada. The federal government has authority over matters pertaining to federal civil servants, federal crown corporations, employees of federal chartered organizations and employees in industries where more than one jurisdiction is involved. The provincial governments hold principal responsibility for workers within each province.

Prince Edward Island is the only province which has no provision established for limiting workers exposure to toxic substances. The ACGIH list of TLV®s is directly referenced in the legislation of British Columbia, Manitoba, New Brunswick, Nova Scotia, Newfoundland and the federal government as the

guideline for worker exposure to workplace contaminants. Alberta and Saskatchewan have established exposure standards (in regulations) for TMA in the workplace.

Canada (Federal)

Exposure to dangerous substances falls under the Canada Labour Code, Chapter 997, Part IV, Canada Dangerous Substances Regulations, Section 10 and 11 (see below).

Enforcement of these regulations is by the Department of Labour.

Section 10 - Subject to Section 11, every employer shall ensure that the concentration of any dangerous substance that may be carried by the air in any area where an employee is working (a) does not exceed the threshold limit value recommended by the American Conference of Governmental Industrial Hygienists in its pamphlet "Threshold Limit Values for Air Borne Contaminants 1971", as amended from time to time; or (b) conforms with any standard that:

i) follows good industrial safety practice
ii) is acceptable to the Division Chief

Section 11 - Except in respect of any dangerous substance that is assigned a Ceiling "C" value by the American Conference of Governmental Industrial Hygienists an employer may allow the concentration of a dangerous substance that may be carried by the air in the area where an employee is working to exceed the threshold limit value described in section 10 for a period of time according to a formula

a) prescribed by the American Conference of Governmental Industrial Hygienists or
b) approved in writing by the Division Chief

British Columbia

Exposure to hazardous substances falls under the provisions of two acts, the Worker's Compensation Act and the Factory Act.

a) Worker's Compensation Act, S.B.C. 1968 c.59, Industrial Health and Safety Regulations, B.C. Reg. 585/77 as am. by B.C. Reg. 374/79, Section 13.01(1). Enforced by the Workers' Compensation Board.

   A worker's exposure to airborne contaminants is limited to stated permissible concentrations. No exposure standard for TMA has been provided.

b) Factory Act, R.S.B.C., 1979 c.118, Occupational Environment Regulations, B.C. Reg. 128/74 as am. by Reg. 409/81, Section 6.001. Enforced by the Department of Labour.

   Workers must not be exposed to concentrations of atmospheric contaminants contrary to the TLVs published by ACGIH (used as a guide) or to concentrations specified by an inspector.

Alberta

Exposure to hazardous substances falls under the provisions of the Occupational Health and Safety Act, R.S.A. 1980, c.O-2, R.S.A. 1980, c.15 (supp.), Chemical Hazards Regulation, Reg. 8/82. Enforcement by the Occupational Health and Safety Council.

The prescribed occupational exposure limit for TMA is:

8 hour	TWA	0.05 mg/m^3
15 minutes	TWA	0.15 mg/m^3

Saskatchewan

Exposure to hazardous substances falls under the provisions of the Occupational Health and Safety Act, S.S. 1978, c.O-1, Occupational Health and General Regulations, O in C 567/81 Sask, Reg.1, May 17, 1981, Part VIII, Chemical Substances, Section 73 Appendix VI. This is enforced by the Occupational Health and Safety Branch, Department of Labour.

The employer must ensure that atmospheric contamination of the workplace by chemical substances is kept as low as reasonably practicable and shall ensure that the limits for substances stipulated in Appendix VI are not exceeded in the workplace.

The prescribed limits for trimellite anhydride (sic) are:

8 hour	0.04 mg/m^3 TWA
15 minutes	0.12 mg/m^3 TWA

Manitoba

Exposure to hazardous substances falls under the provisions of the Mines Act, Man. Reg. 254/73, Part IV (General Safety Requirements) Section 4.22(2). Enforced by the Department of Mines and Natural Resources.

Exposure limits in Manitoba are those set out by ACGIH - published in its updated pamphlet, "Threshold Limit Values for Chemical Substances in Workroom Air as amended from time to time".

The Safety and Health Inspectorate Workplace Health and Safety Division enforces the ACGIH TLV's.

Quebec

Exposure to hazardous substances falls under the Environment Quality Act, S.Q. 1972, c.49, Regulations respecting the quality of the work environment, o.c. 3845-80, as am. by o.c. 576-82, Schedule "A" (Permissible Concentration of Gases, Dusts, Fumes or Mists in the Work Environment). Enforced by the Occupational Health and Safety Commission.

Quebec's "Act Respecting Occupational Health and Safety" introduced in 1979 has not prescribed exposure limits for TMA in the workplace.

New Brunswick

Exposure to hazardous substances falls under the provisions of the Occupational Safety Act, S.N.B. 1976, c.o.-0.1 Regulation (as am. by N.B. Reg. 77-79, 77-92, 78-53 and 80-82) Section 8(4). This is enforced by Occupational Health and Safety Commission established under the Occupational Health and Safety Commission Act, 1980.

"The employer shall ensure that where the air in working areas may be contaminated, which may constitute a hazard to the health and safety of employees the concentration of such substance shall not exceed the threshold limit value recommended by the American Conference of Governmental Industrial Hygienists in its pamphlet..."

Prince Edward Island

Exposure to hazardous substances in this province is not regulated. Under the Public Health Act, S.P.E.I., 1980 c-42 Section 23(1), the Department of Public may make regulations

with respect to "...protective standards and measures to prevent or reduce dangers to personal health related to the work environment".

Nova Scotia

Exposure to hazardous substances falls under the Health Act, R.S.N.S. 1967, c.247 Regulations (O in C 76-1510), Section 4(1). It is enforced by the Occupational Health Division, Department of Public Health.

The occupational health standard relating to gases, vapours, mists, fumes, smoke, dust and other chemical substances and physical agents is as shown in the 1976 list, published by the American Conference of Governmental Industrial Hygienists and its subsequent amendments or revision.

Newfoundland

Exposure to hazardous substances falls under the Occupational Health and Safety Act, R.S.N. 1978, c.23, Occupational Health and Safety Regulations Nfld. Reg. 104/79, Section 25(5)(a). It is enforced by the Occupational Health and Safety Division.

The employer shall ensure that atmospheric contamination of the workplace by chemical substances is kept as low as is reasonably practicable and in the case of substances for which a threshold limit value is currently established by the "ACGIH" that threshold value shall not be exceeded.

8.3 Other Countries

United States

In the United States, a recommended exposure limit for TMA or 0.04 mg/m^3 (TWA) has been set out by ACGIH. No STEL value has been established for TMA.(57) NIOSH has recommended at this time that TMA be handled as an extremely toxic agent in the workplace.(10)

AMOCO Chemicals Corporation, a subsidiary of Standard Oil Company of Indiana and sole producer of TMA, recommends that no one be exposed to respirable TMA dust or fumes exceeding levels of 0.05 mg/m^3 of air (TWA) during an 8 hour work day.(58)

Europe

The European Economic Community has recommended labelling, with a statement that TMA is an irritant.(1)

In Sweden, a ceiling value of 0.04 mg/m^3 has been set. The limit is based on classification of TMA as a sensitizing agent(61).

The limit in the Federal Republic of Germany is 0.04 mg/m^3 of TMA as a maximum average concentration for a 8 hour day(62).

Norway has a limit, set in 1981, of 0.04 mg/m^3 for an 8 hour day(63).

In the U.K., the ACGIH list is adopted almost entirely, including the TLV® for TMA (0.04 mg/m^3)(64).

Several countries use the ACGIH TLV® as a guide; these include Australia, Belgium and the Netherlands(65). In these cases, the ACGIH value, 0.04 mg/m^3 TWA, would apply.

Limits in different jurisdictions are summarized in Table 7.

TABLE 7
OCCUPATIONAL EXPOSURE LIMITS FOR TMA
IN OTHER JURISDICTIONS

Jurisdiction	Limit for 8 Hours	Guideline or Regulation
CANADA	0.04 mg/m^3 (ACGIH, current)	Regulation
Ontario	0.039 mg/m^3	Criteria for Discussion
Alberta	8 hour TWA - 0.05 mg/m^3 15 minute TWA - 0.15 mg/m^3	Regulation
British Columbia	0.04 mg/m^3 (ACGIH, unstated date)	Regulation
Manitoba	0.04 mg/m^3 (ACGIH, current)	Regulation
New Brunswick	0.04 mg/m^3 (ACGIH, unstated)	Regulation
Newfoundland	0.04 mg/m^3 (ACGIH, current)	Regulation
Nova Scotia	0.04 mg/m^3 (ACGIH, current)	Regulation
Prince Edward Island	None prescribed	-
Quebec	None prescribed	-
Saskatchewan	8 hour TWA - 0.04 mg/m^3 15 minute TWA - 0.12 mg/m^3	Regulation
UNITED STATES		
OSHA	No numerical standard	
NIOSH	No numerical recommendation	
ACGIH	0.04 mg/m^3	Recommendation
Federal Republic of Germany	0.04 mg/m^3	Regulation
Norway	0.04 mg/m^3	Regulation
Sweden	0.04 mg/m^3 (Ceiling)	Regulation
U.K.	0.04 mg/m^3 (ACGIH)	Guidance Note

9. OPTIONS FOR REGULATORY CONTROL

9.1 Introduction

In this section the options available to the Ministry for development of a regulatory strategy for trimellitic anhydride exposure are reviewed. The strategy may include components such as:

- monitoring, both air and medical
- exposure reduction methods
- exposure limits
- regulatory structure-guidelines or regulation (or "other").

Factors to consider include present and potential health hazard aspects, current practices in the Province and in other jurisdictions, and technical and economic feasibility of alternative methods.

9.2 Exposure Controls

Engineering controls amenable to use with TMA include:

- process segregation
- local ventilation
- special batch loading
- procedures (bulk containers, special hoppers)
- empty container handling procedures

The first three are routinely used in Ontario. They do not provide adequate protection against TMA exposure. Even with such systems, respiratory, eye, and possibly skin protection are needed. However, considering the low TWAEC for TMA

without good local ventilation, adequate worker protection might not be possible with any practical level of personal protection. Prevention of more widespread contamination is enhanced by segregation of the (loading) process. The use of aprons and coveralls prevents clothing contamination. Good housekeeping procedures are all important.

Administrative controls are not a feasible approach to protection from TMA; the excursion levels measured have been too high for time-of-exposure reduction to be a satisfactory health measure.

The use of personal protection does not appear avoidable in isolating the worker's target organs from TMA. The combination of a very low exposure criterion, brief exposures characterized by high levels of poorly-controllable dust and a high level of discomfort associated with exposure encourages acceptance of personal protection. More continuous or more frequent use would probably not be acceptable and would lead to non-compliance. With the focus of personal protection on the respiratory system, the problem of eye irritation may be compounded. Respirators tend to interfere with goggles and other eye protection. To eliminate both problems full-face masks would be required. At present these are not widely used.

A requirement for specific training in the TMA hazards and its avoidance may be considered. Currently, safety data sheets and handling procedures are made available, along with any precautions outside the chemical industry's normal practice. For occasional users, this may be sufficient. For regular users, this is not the case. Where exposure is continuous, more specific training appears to be indicated.

9.3 Monitoring

Sampling of air for TMA has been conducted in only one way, using a sampling pump and dust collector. This is suited to both area and personal monitoring. Analysis, however, may be done using two slightly different techniques: gas-liquid chromatography (GLC) and high performance liquid chromatography (HPLC). The choice depends on the concentrations expected and/or the duration of exposure. The literature indicates that HPLC methods published are more sensitive, and usable at lower concentrations than GLC. A second consideration is instrument availability, which tends to favour GLC. Reliability of method is not cited as a major constraint.

Medical monitoring of workers is at present still a research activity. The major immunologic researchers in the TMA-disease field have developed tests that can distinguish between symptomatic and asymptomatic workers, and are perhaps capable of indicating potential for sensitization. The thrust of the tests is as diagnostic rather than preventative and thus the potential for value as a routine measuring technique appears limited.

A periodic medical checkup is a common requirement in these industries and includes blood and urinalysis, pulmonary function testing and chest X-rays. This requirement is advisable for TMA.

9.4 Exposure Limit

Specifically assigned limits for TMA exposure are not widespread; those in use are close to Amoco's recommendation for

protection of sensitized workers, based on eight-hour time weighted average exposures. The options available to the Ministry for regulating exposures are:

- continue using the TWAEC, 0.039 mg/m^3
- use the ACGIH value, 0.04 mg/m^3 (eight hour)
- use the Amoco recommendation 0.05 mg/m^3 (eight hour)
- assign an exposure limit that recognizes the short-term nature of much TMA exposure, such as is done in Saskatchewan or Alberta (15 minute limits then are 0.12 and 0.15 mg/m^3 respectively)
- assign a ceiling limit

Although data on the levels at which sensitization may occur are sparse, values in the range 0.039 to 0.05 mg/m^3 have been provisionally cited as limits suitable for susceptible individuals.(1,13) No comments on this limit were received from those surveyed.

Adoption of a higher short-term exposure limit could be defended, on the basis that eight hour exposure is not representative of Ontario experience, and a higher level might be tolerated for brief periods. Conversely, there is no firm data on the levels required to produce sensitization, and selecting a significantly higher limit for short-term exposure could increase the risk of both sensitization and irritant effects. Setting a ceiling for exposure runs the same risks.

The type of limit to be set may also be considered as a function of measurement technique. Current sampling methods take about an hour per sample. A ceiling implies an instantaneous concentration limit, which is not measurable with current technology. Since one hour samples are the shortest currently routinely done, compliance with a limit based on a shorter time period, at present at least, cannot be consistently demonstrated.

9.5 Regulatory Structure

The survey of Ontario TMA users indicated the following preferences for regulatory control of TMA exposure:

Voluntary Exposure Limit	43%
Mandatory Exposure Limit	29%
Technically beyond the company's judgement. If TMA is truly a serious hazard it should have a comprehensive standard with mandatory medical examination, record keeping, monitoring and exposure limit requirements	14%
Voluntary exposure limit bearing some relationship to frequency and quantity of use	14%

Most manufacturers would be able to comply with a regulated limit of 0.04 mg/m^3 averaged over eight hours or more, but do not appear able to meet this consistently if averaged over an hour or less.

Features that might be included in a guideline or regulation are:

- Classification of TMA as a sensitizing agent or allergen
- Exposure limits - eight hours, short-term, or ceiling
- Requirements for air monitoring
- Requirement for training or instruction in the hazards of TMA use
- Requirements for controls; engineering and personal protection
- Requirements for medical examinations
- Requirements for record keeping, both for exposure records and medical records
- Requirements for warning signs
- Reporting of exposures resulting in worker health effects
- A "small user" or "infrequent user" provision, to reduce administrative burden on small users

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APPENDIX I

TRIMELLITIC ANHYDRIDE (TMA)

QUESTIONNAIRE

1. a) Name of Establishment _____

   b) Head Office Address _____

   _____

   _____

   c) Ontario Plant Sites _____

   d) Number of Employees _____

   e) Questionnaire Completed by

   Name Position Telephone

   _____

2. a) Amount of trimellitic anhydride used annually _____

   b) Frequency of use: (check appropriate category)

   i) continuous ☐
   ii) daily ☐
   iii) one day per week ☐
   iv) one day per month ☐
   v) other (specify) ☐ _____

   c) What containers do you handle? (check appropriate category)

   i) 25 kg bags ☐
   ii) 200 L drums ☐
   iii) bulk containers ☐
   iv) others (specify) ☐ _____

3. a) How many plant employees are directly involved in trimellitic anhydride use?

	Number of Workers	% of Total Work Force
Through regular use		
In case of leak or spill		

Occupational Category	No. of Workers	Duration of Exposure, e.g. full shift, occasional walk through, process upset, etc.
Operating crew	_____	_____
Maintenance	_____	_____
Material handling	_____	_____
	_____	_____
Other (specify)	_____	_____

MONITORING

4. What processes or procedures are likely to result in worker exposure to trimellitic anhydride (including fugitive emissions and spills)?

_____

_____

_____

_____

_____

5. a) Does your firm monitor worker exposure to trimellitic anhydride? YES ☐ NO ☐

b) How frequently? _____

c) What type of sampling is conducted?

Personal _____ Work Area _____

d) How are the samples collected?

_____

_____

_____

_____

_____

e) What levels have been found?

Personal Samples: Maximum _____ Minimum _____ Average _____

Area Samples: Maximum _____ Minimum _____ Average _____

6. Location and Nature of Sampling

Process	Sampling Location	Sampling Technique	Number and frequency of samples	Sampling Duration	Exposure Levels (Average)	Exposure Levels (Maximum)

7. What method of sample analysis is used? _____
If samples are analyzed by an independent laboratory, give name and address

_____

_____

8. Total costs for sampling and analysis for trimellitic anhydride for most recent year available.

$_____ Year _____

MEDICAL MONITORING

9. a) Are pre-employment medical examinations conducted for employees who will be working with trimellitic anhydride? YES ☐ NO ☐

   b) Which of the following are included in the pre-employment medical examination? (check appropriate category(s))

   i) work history ☐
   ii) medical history ☐
   iii) blood analysis ☐
   iv) other (please describe) ☐ _____

   _____

10. a) Are periodic medical examinations conducted for employees exposed to trimellitic anhydride? YES ☐ NO ☐

    b) What items are included in the periodic examinations? (indicate frequency after each item)

	Frequency
Blood Analysis	
Other (please describe)	

11. a) What medical personnel are available in your firm?

	Physician	Nurse	Other (specify)
Full-time	_____	_____	_____
Part-time	_____	_____	_____
Contract	_____	_____	_____
Fee-for-Service	_____	_____	_____
Other	_____	_____	_____

    b) What are the total annual costs for medical examinations and tests? $_____

12. a) Are medical records maintained for employees exposed to trimellitic anhydride? YES ☐ NO ☐

    b) Are medical records maintained for former employees who worked with trimellitic anhydride? YES ☐ NO ☐

    c) What are the total annual costs of maintaining medical records? $_____

EXPOSURE CONTROL PROCEDURES

13. a) Which of the following methods are used in your plant to limit worker exposure to trimellitic anhydride?

	YES	NO
Worker rotation		
Transfer of over-exposed workers to trimellitic anhydride free areas		
Limitation of production time of trimellitic anhydride-using products		
Others (please describe)		

14. a)(i) What personal protective equipment is available in your plant for workers exposed to trimellitic anhydride?

TYPE	PROCESS	WHEN USED	MANDATORY OR OPTIONAL	# OF WORKERS AFFECTED
respirators: type:				
face shield				
safety goggles				
overalls				
gloves				
aprons				
other (specify)				

(ii) Is non-compliance (non-use) a problem? YES ☐ NO ☐

(iii) Is equipment checked, maintained and replaced regularly? YES ☐ NO ☐

Frequency _____

(iv) What are total costs to your firm for personal protective equipment and clothing for the control of trimellitic anhydride exposure? (include costs for routine equipment inspection and maintenance) $_____

14. b)(i) What hygiene/first-aid facilities are provided in your plant for workers exposed to trimellitic anhydride?

FACILITY	YES	NO	USED AS REQUIRED OR RECOMMENDED	
			YES	NO
deluge showers in plant				
eyewash fountains				
first-aid stations				
changerooms with shower and locker facilities				
laundry services supplied				
separate lunchrooms				
clean storage area, for personal protective equipment				
other (specify)				

(ii) What are the annual costs to your firm for hygiene/ first-aid facilities? (include costs for repairs and maintenance) $_____

15. Please supply the following information on engineering controls presently in place to reduce worker exposure to trimellitic anhydride. (Give only that portion of the cost which is incurred in controlling worker exposure to trimellitic anhydride).

CONTROL DEVICE	PROCESS	YEAR OF INSTALLATION	CAPITAL COST	ANNUAL OPERATING EXPENSES
Local exhaust ventilation				
Process change (specify)				
Other (specify)				

16. a) Are there any substitutes for trimellitic anhydride that could be used in your operation? YES ☐ NO ☐

If so, what are they? _____

b) Are they economically feasible? YES ☐ NO ☐

c) Do they have other disadvantages (fire hazard, toxicity)? YES ☐ NO ☐

17. What strategy would you like to see the government introduce for the control of worker exposure to trimellitic anhydride? (check appropriate choice)

i) Voluntary Exposure Limit ☐ _____

ii) Mandatory Exposure Limit ☐ _____

iii) A comprehensive standard with mandatory medical examination, record keeping, monitoring and exposure limit requirements ☐ _____

iv) Other (please describe). ☐ _____

18. What would be the economic impact of these various control strategies on your company?

_____

_____

EMPLOYEE EDUCATION AND TRAINING

19. a) Does your firm provide health and safety education and training for all employees who may be exposed to trimellitic anhydride on the job? YES ☐ NO ☐

b) Briefly describe the training and education program offered (include content and length of classes, films, availability of written materials, frequency of training sessions).

_____

_____

_____

_____

_____

_____

_____

c) Is any special education given to health and safety committee members re specific hazards? YES ☐ NO ☐

20. Are warning signs posted in areas where exposure to trimellitic anhydride may occur? YES ☐ NO ☐

21. Do you provide workers with chemical safety data sheets? YES ☐ NO ☐

WORKER CONCERNS

22. a) Have any general concerns been raised by employees about trimellitic anhydride exposure or about illnesses possibly related to it? YES ☐ NO ☐

If yes, specify_____

_____

b) How were the concerns raised?

Health and Safety Committee ☐
Union representative ☐
Directly to management ☐
During Ministry inspections ☐

c) Have actions been taken as a result?

Specify _____

_____

LIST OF ORGANIZATIONS CONTACTED DURING TRIMELLITIC ANHYDRIDE STUDY

TMA USERS	USE

Ashland Chemicals
2620 Royal Windsor Drive
Mississauga, Ontario
L5J 4E7

President: Mr. B.R. Wakeford
Telephone:

BASF Canada Inc.
Cornwall Works
501 Wallrich Avenue
Cornwall, Ontario
K6J 2B5

Works Manager: Mr. G. Creedy
Telephone:

Benjamin Moore and Company Limited
15 Lloyd Avenue
Toronto, Ontario
M6N 1G9

President: Mr. J. Sobie
Telephone:

H.L. Blachford Limited
2323 Royal Windsor Drive
Mississauga, Ontario
L5J 1K5

President: Dr. J. Blachford
Telephone:

Blandford Insulation Limited
5100 Maingate Drive
Unit 11
Mississauga, Ontario
L4W 1X6

President: Mr. J.R. Blandford
Telephone:

LIST OF ORGANIZATIONS CONTACTED
DURING TRIMELLITIC ANHYDRIDE STUDY
(continued)

TMA USERS	USE

Canada Wire and Cable Limited
250 Ferrand Drive
Don Mills, Ontario
M3C 3J4

President & Chief Executive Officer: Mr. B.T. Ness
Telephone:

Canadian Paint & Coatings Association
515 Ste. Catherine West
Suite 825
Montreal, Quebec
H3B 1B4

President: Mr. M. Bradley
Telephone:

CIL Inc.
P.O. Box 200
Station "A"
Willowdale, Ontario
M2N 6H2

President: Mr. C.H. Hantho
Telephone:

Energy & Chemical Workers Union
603 Argus Road
Oakville, Ontario
L6J 6G6

Ontario Coordinator: Mr. K.V. Rogers
Telephone:

Glidden Company Limited
351 Wallace Avenue
Toronto, Ontario
M6P 3N9

Vice-President & Managing Director: Mr. A.D. Ross
Telephone:

LIST OF ORGANIZATIONS CONTACTED DURING TRIMELLITIC ANHYDRIDE STUDY (continued)

TMA USERS	USE

Iroquois Chemicals Limited
P.O. Box 399
Cornwall, Ontario
K6H 5T1

President: Mr. D. Segur
Telephone:

Mobil Chemical Canada Ltd.
Coatings Division
645 Coronation Drive
West Hill, Ontario
M1E 4R6

Vice-President & General Manager: Mr. R.G. Hoffman
Telephone:

Monsanto Canada Inc.
P.O. Box 787, Streetsville
Mississauga, Ontario
L5M 2G4

President: Mr. W.W. Lorenz
Telephone:

Ontario Federation of Labour
15 Gervais Drive
Don Mills, Ontario
M3C 1Y8

President: Mr. C. Pilkey
Telephone:

PPG Industries Canada Ltd.
50 St. Clair Avenue West
Toronto, Ontario
M4V 1M9

President: Mr. D.R. Pepall

LIST OF ORGANIZATIONS CONTACTED DURING TRIMELLITIC ANHYDRIDE STUDY (continued)

TMA USERS	USE

Schenectady Chemicals Canada Ltd.
319 Comstock Road
Scarborough, Ontario
M1L 2H3

General Manager: Mr. Rod Morris
Telephone:

Sterling Limited
P.O. Box 554
St. Catharines, Ontario
L2R 6X1

President: Mr. J.E. Hanson
Telephone:

United Steelworkers of America
100 Lombard Street, 4th Floor
Toronto, Ontario
M5C 1L4

Director: Mr. David Patterson
District No.6
Telephone:

APPENDIX II

SCALE OF WEIGHTED SCORES FOR GRADING THE SEVERITY OF OCULAR LESIONS

APPENDIX II

SCALE OF WEIGHTED SCORES FOR GRADING THE SEVERITY OF OCULAR LESIONS

I. CORNEA

A. Opacity - Degree of Density (area which is most dense is taken for reading)

Scattered or diffuse area - details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4

B. Area of Cornea Involved

One quarter (or less) but not zero	1
Greater than one quarter-less than one-half	2
Greater than one-half less than three quarters	3
Greater than three quarters up to whole area	4

Score equals A X B X 5 Total maximum = 80

II. IRIS

A. Values

Folds above normal, congestion, swelling, circumcorneal injection (any one or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage; gross destruction (any one or all of these)	2

Score equals A X 5 Total possible maximum = 10

APPENDIX II

SCALE OF WEIGHTED SCORES FOR GRADING THE SEVERITY OF OCULAR LESIONS

(continued)

III. CONJUNCTIVAE

A. Redness (refers to palpebral conjunctivae only)

Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

B. Chemosis

Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of the lids	2
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

C. Discharge

Any amount different from normal (does not include small amount observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to the lids	2
Discharge with moistening of the lids and considerable area around the eye	3

Score (A + B + C) X 2 Total maximum = 20

The maximum total score is the sum of all scores for the cornea, iris and conjunctivae.

FROM:

Draize, J.H., G. Woodard, H.O. Calvery. 1944. "Methods for the Study of Irritation and Toxicity of Substances applied topically to the Skin and Mucous Membranes", J. Pharmacol. Exp. Ther. 82:377-390.

APPENDIX III

NOISH QUALIFICATION CRITERIA
FOR
ANALYTICAL METHODS

APPENDIX III

NIOSH differentiates analylical methods using the following "Classification of Analytical Methods".

Class A - Recommended

A method which has been fully evaluated and successfully collaboratively tested by a selected group of laboratories.

Class B - Accepted

Subjected to a thorough evaluation procedure in the NIOSH laboratory and found to be acceptable.

Class C - Tentative

A method which is wide use and which has been adopted as a standard method or recommended by another Government agency or one of several professional societies such as ACGIH, AOAC, AIHA, ASTM or ISC.

Class D - Operational

A method in general use or approved by most professional industrial hygience analysts but which has not been thoroughly evaluated by NIOSH or any professional society.

Class E - Proposed

A new, unproved or suggested method not previously used by industrial hygiene analysts but which gives promise of being suitable for the determination of a given substance.

(NOISH Manual of Analytical Methods, Second Edition, Volume 1, 1977 by Crable, J.V. and D.G. Taylor, NIOSH, Cincinnati, Ohio)

APPENDIX IV

TRIMELLITIC ANHYDRIDE

Measurement Support Branch

Analytical Method

Analyte:	Trimellitic Anhydride*	Method No:	P&CAM 322
Matrix:	Air	Range :	0.048 - 0.24 mg/m^3
Procedure:	Filter collection, extraction derivatization, GC-FID	Precision:	0.087
Date Issued:	8/29/80		
Date Revised:		Classification:	E (Proposed)

1. Synopsis

Trimellitic anhydride (TMA) is collected from air on a PVC-copolymer membrane filter. The filter is extracted with methanol and the methanol volume is reduced by evaporation. Boron trifluoride/methanol is added to the extract to derivatize the anhydride. The mixture is heated at 97°C for 20 minutes during which the anhydride is converted to its trimethyl ester. After cooling the boron trifluoride is complexed and precipitated with a pyridine/pentane/ether mixture. An aliquot of the mixture is injected and analyzed by a gas chromatograph equipped with flame ionization detector. The concentration of unknown samples is determined from a calibration curve.

2. Working Range, Sensitivity and Detection Limit

2.1 The working range is from 0.048 - 0.24 mg/m^3 for a 400-L air sample corresponding to 19.2 - 96/µg sample.

2.2 The detection limit was not determined, but it is estimated to be on the order of 2 µg per 5 µL injection at 8 x 10 attenuation using F.I.D.

3. Interferences

3.1 When interfering compounds are known or suspected to be present in the air, such information, including their suspected identities should be transmitted with the sample.

---

*1,2,4-Benzenetricarboxylic acid-1,2-anhydride

3.2 Any compound that has the same retention time as the trimethyl ester of trimellitic anhydride at the operating conditions described in this method is an interference. The interference may be eliminated by changing the operating conditions of the chromatograph, e.g. by changing the temperature programming or carrier gas flow-rate.

3.3 This method will not differentiate between trimellitic anhydride and trimellitic acid. Under derivatization both compounds will form the same trimethyl ester (trimethyl trimellitate).

4. Precision and Accuracy

The analytical pooled relative standard deviation (RSD) is 8.7% determined from 15 TMA spiked PVC-copolymer filters over the range of 19.2-96 ug/filter. The average recovery is 103.3%. Calibration standards (n=21) exhibited an RSD of 7.6%.

5. Advantages and Disadvantages

5.1 The method offers a one step derivatization procedure in which the anhydride directly converts into its corresponding trimethyl ester.

5.2 The method has a low detection limit, 2 ug.

5.3 Trimellitic anhydride recoveries are quantitative with acceptable precision.

5.4 After derivatization, samples are stable for at least two days. The retention time of the ester is approximately 7.5 minutes.

5.5 The method may be used as a general method for other higher molecular weight organic anhydrides and carboxylic acids.

5.6 See Section 3.3.

6. Apparatus

6.1 Air Sampling Equipment

6.1.1 Polyvinyl chloride-copolymer membrane filters, 0.8 um in pore size, 37-mm in diameter, Gelman DM-800 or equivalent.

6.1.2 Plastic three piece 37-mm filter holders (cassettes). The filter is supported in the cassette by a cellulose backup pad.

6.1.3 A personal air sampling pump capable of operating at 1.5 to 2.0 liters per minute.

6.1.4 A thermometer, barometer and a stopwatch.

6.2 Analytical Equipment

6.2.1 Gas chromatograph equipped with a flame ionization detector (FID) and glass-lined injection port.

6.2.2 A stainless-steel column, 9' (274 cm), 2-mm I.D. packed with 60/80 mesh Tenax-GC (Applied Science Labs., Inc., State College, PA.) or equivalent porous polymer packing. No liquid stationary phase is needed.

6.2.3 A strip-chart recorder, 1mV full scale.

6.2.4 Test tubes, glass 13 x 100-mm size with Telfon lined screw caps. Rubber lined caps produce extraneous peaks. Pyrex # 9082

6.2.5 Glass syringe, 10 µL.

6.2.6 Pipettes, 10 µL, 25 µL, 50 µL, variable 50-250 µL and 0.25-5 mL.

6.2.7 Volumetric flask, 250 mL.

6.2.8 Beakers, 50 mL and 250 mL.

6.2.9 Hot plate, variable heat settings.

6.2.10 Watch glasses to fit on 50 mL beakers.

6.2.11 Ultrasonic bath.

6.2.12 Air evaporator/concentrator (6 syringe manifold block for reducing the methanol volume in the test tubes).

6.2.13 High temperature GC injection septa (350°C).

6.2.14 Analytical balance, to ± 0.01 mg.

6.2.15 Tweezers, flexible tubing, applicator stick, weighing paper.

7. Reagents

Whenever possible, reagents used should be ACS reagent grade or better.

7.1 Methanol.

7.2 Pentane.

7.3 Diethyl ether.

7.4 Boron trifluoride/methanol, 14% w/v mixture (commercially available from GC supplier).

7.5 Pyridine.

7.6 Pyridine mixture. Prepare a 7:3 pyridine/pentane mixture in a screw-cap tube.

7.7 Trimellitic anhydride (1,2,4-Benzenetricarboxylic anhydride).

7.8 Laboratory compressed-air.
Helium

8. Procedure

8.1 Cleaning of Equipment. All glassware used for the laboratory analysis should be detergent washed and thoroughly rinsed with tap water and distilled water.

8.2 Calibration of Personal Pumps. Each personal pump must be calibrated with a representative filter cassette in the line. This will minimize errors associated with uncertainties in the sample volume collected.

8.3 Collection and Shipping of Samples

8.3.1 Assemble the filter in the three-piece filter cassette holder and close firmly to insure that the center ring seals the edge of the filter. The PVC-copolymer membrane filter is supported by a cellulose backup pad and the filter holder is held together by plastic tape or a shrinkable cellulose band. If the filter does not lie flat on the backup pad and the spacer ring does not fit snugly into the bottom of the filter holder, sample leakage will occur around the filter. Remove the cassette plugs. Use a piece of flexible tubing to connect the filter holder to the pump.

8.3.2 Clip the cassette to the worker's lapel. Air being sampled should not be passed through any hose or tubing before entering the filter cassette.

8.3.3 A sample size of 400 liters is recommended. Sample at a flow rate of 1.7 liters per minute for 4 hours. The flow rate should be known with an accuracy of at least $\pm$ 5%. A high volume air sample may also be submitted along with the other personal samples for qualitative GC work.

8.3.4 Turn the pump on and begin sample collection. Since it is possible for filters to become plugged by heavy particulate loading or by the presence of oil mists or other liquids in the air, the pump rotameter should be observed frequently, and the sampling should be terminated at any evidence of a problem.

8.3.5 Terminate sampling at the predetermined time and note sample flow rate, collection time and ambient temperature and pressure. If pressure reading is unavailable, record the elevation. Replace filter plugs.

8.3.6 Blank. With each batch of ten samples submit at least one filter from the same lot of filters which was used for sample collection and which is subjected to the same handling as for the samples except that no air is drawn through it. Label this as a blank.

8.3.7 Shipping. The filter cassettes should be plugged and shipped in a suitable container, designed to prevent damage in transit.

8.4 Analysis of Samples

8.4.1 Extraction

Place a field or a spiked filter sample in a 50-mL beaker and add 3 mL methanol. Put a watch-glass on the beaker and place beaker on a hot plate (65°C) for one minute. Remove beaker and place it in the ultrasonic bath for one minute (watch-glass is still on the beaker to prevent sample loss and water contamination of the sample during ultrasonication).

Rinse the bottom of the watch glass with 1 mL methanol and collect the rinse in the beaker. Lift the filter with tweezers above the methanol level and rinse both sides of the filter slowly with two 3-mL aliquots of methanol, collecting the rinse in the same beaker. Roll and squeeze the filter with tweezers against the inside wall of the beaker to remove methanol retained by the filter, then discard the filter.

Place the beaker on the hot plate (55°C) and reduce the methanol level to less than 5 mL. Transfer the methanol extract to a test tube. Rinse the beaker two or three times with small amounts of methanol and combine the rinsings in the test tube. Evaporate the methanol in the test tube to near dryness (about 10 µL) by blowing warm air over the surface with the use of the evaporator block. For comparison, 10 µL methanol may be added to an empty test tube to observe the amount of 10 µL. The sample is now ready for derivatization.

8.4.2 Derivatization

To each sample or standard tube that contains an anhydride sample, add 125 µL BF_3/methanol. Screw the cap tightly and place the tube in a water bath (97°C) for 20 minutes. Remove tube and let it cool to room temperature. Add the following solvents to the tube: 50 µL diethyl ether, 50 µL pentane, and 50 µL of the pyridine mixture. Between solvent additions screw the cap on each tube to prevent evaporation of the solvents. Shake tube mildly between additions. (With the pyridine addition a white precipitate forms, which is a complex of BF_3· pyridine.) After a few minutes the white material precipitates and the sample is ready for analysis. No centrifuging is necessary.

8.4.3 Gas Chromatographic Conditions

Column:	See Section 6.2.2
Column Temperature Program:	250°C for 2 minutes, then 16°/min to 310°C, hold for 4 min. at 310°C

Injection Temperature:	315°C
Detector Temperature:	325°C
Helium Flow Rate:	35 mL/min
Hydrogen Flow Rate:	53 mL/min
Air Flow Rate	550 mL/min
Detector:	FID, Attenuation 16 x 10 and 32 x 10
Injection Volume:	5 µL
Retention Time:	7.5 minutes

The FID collector ring may need to be cleaned once in a while with methanol to remove white deposit.

8.5 Filter Recovery Determination

8.5.1 Spiking Solution. Prepare a stock solution of 0.01 M trimellitic anhydride (1.92 µg / µL) by dissolving 0.4803 g TMA in a 250 mL volumetric flask containing methanol and making up the remaining volume with methanol.

8.5.2 Spike six PVC-copolymer filters for each level using pipettes. Use 10, 25, and 50 µL volumes of the spiking solution to get 19.2, 48, and 96 µg TMA on each filter respectively. When each filter is dry, follow Section 8.4 to analyze the sample.

8.5.3 Percent recovery (R, extraction efficiency) is determined as follows:

$$R = \frac{W_r}{W_s} \times 100$$

where: W_r = micrograms recovered

W_s = micrograms spiked

Convert peak area to micrograms from the equation of the calibration curve.

9. Calibration and Standardization

9.1 Using the 0.01 M TMA solution from 8.5.1, prepare 6 calibration standards per level by pipetting 10, 25, and 50 µL into test tubes. This is equivalent to 19.2, 48, and 96 µg TMA per each level. Be sure to screw the caps on the tubes between additions. Follow Section 8.4.2 to derivatize the standards.

9.2 Since the total volume in each tube after derivatization is different- 285, 300, and 325 µL for 19.2, 48, and 96 µg level respectively - a correction for the areas must be made. Use the factors of 1.053 and 1.14 to multiply the areas of the standards at the 48 and 96 µg levels respectively.

9.3 Prepare a plot of the corrected areas of the standards versus concentration of TMA. Do statistical analysis of "least squares" to determine the equation of the calibration curve.

9.4 Suggestion: It was found, after the method was completed, that since no sample loss occurred even when the sample was completely evaporated, that one may eliminate the correction factors and the evaporation of field samples to 10 µL by completely evaporating to dryness standards and field samples and carrying out the normal procedure from there on.

10. Calculations

10.1 The concentration of unknown TMA samples can be determined graphically from the plot of peak areas of the standards versus concentration.

10.2 The concentration of unknown TMA samples may also be determined from the equation of line obtained from "least squares" statistical analysis

$$C = \frac{A - Y}{M}$$

where: C = concentration of TMA in µg/sample

A = peak area of the sample

Y = line intercept value (from least squares)

M = line slope value (from least squares).

10.3 For personal pumps with rotameters only, the following correction for air volumes sampled should be made:

$$\text{Corrected volume} = F \times T \left(\frac{P_1}{P_2} \times \frac{T_2}{T_1} \right)^{\frac{1}{2}}$$

where: F = sample flow rate

T = sampling time

P_1 = pressure during calibration of sampling pump in mm Hg

P_2 = pressure of air sampled in mm Hg

T_1 = temperature during calibration of sampling pump (^oK)

T_2 = temperature of air sampled (^oK)

10.4 The concentration of trimellitic anhydride in air (C_A) can be expressed in mg/m^3

$$C_A = \frac{W}{V}$$

where: W = weight of field sample in µg

V = volume of air sampled in liters

11. References

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11.2 NIOSH Current Intelligence Bulletin # 21, "Trimellitic Anhydride", Publication No. 78-121.

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John Palassis

Measurement Services Section

APPENDIX V

Determination of Trimellitic Anhydride (TMA) in Factory Atmospheres by High Performance Liquid Chromatography

10185

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Key Words:

High performance liquid chromatography
Ion-pair
Trimellitic anhydride
Air sampling

Introduction

Trimellitic anhydride (1,2,4-benzene tricarboxylic anhydride) (TMA) is used in the polymer industry in the production of plasticisers, as a hardener in epoxy resin formulations, and in many water-soluble paint resins and surface coating systems. A number of the epoxy resin and surface coating systems, containing between 2%-10% TMA, are available as dry powder formulations and are intended for application either by electrostatic dry powder spraying or by dipping pre-heated articles into fluidised beds. Primary occupational exposure to TMA may occur from inhalation of airborne dust and fume when the bulk material is handled or during the application of dry powder formulations to surfaces.

Trimellitic anhydride has been reported to be a severe respiratory irritant and to cause pulmonary edema, immunological sensitisation and asthma-like symptoms [1-3]. Severe respiratory symptoms have been reported during the spray application of dry powder formulation containing TMA [4].

Trimellitic anhydride has recently been assigned a low threshold limit value of 40 μg/m³ by the American Conference of Governmental Industrial Hygienists (ACGIH).

This paper describes a fast quantitative method for the measurement of trimellitic anhydride in factory atmospheres using bonded phase ion-pair chromatography and ultra-violet detection.

Experimental

Reagents and Materials

Acetonitrile (HPLC grade) was obtained from Rathburn Chemicals Ltd, Peebleshire, Scotland. Tetrabutylammonium phosphate was obtained as PIC Reagent A from Waters Asso-

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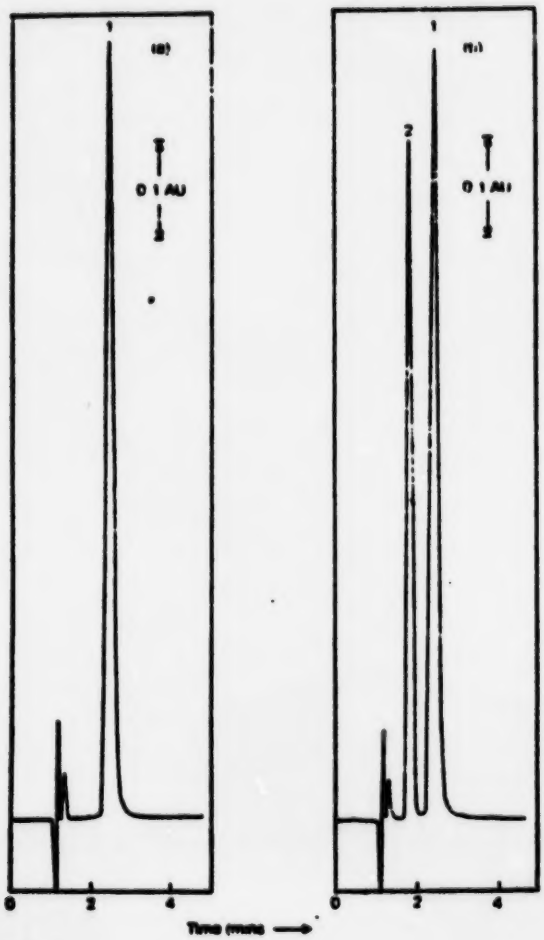

Figure 1

Chromatograms obtained from GF/A filter extracts.
Filters spiked with (a) TMA (b) TMA and phthalic anhydride (PA) and extracted with 1 M NaOH. (1) TMA;(2) PA.

ciates, Cheshire, Great Britain. Trimellitic anhydride was obtained from Aldrich Chemical Company Ltd, Dorset, Great Britain. Glass fibre filters, Type-GF/A, were obtained from Whatman Lab. Sales, Kent, Great Britain.

Mobile Phase

The mobile phase used in this study, was prepared by adding the contents of two PIC reagent A bottles to 500 ml of distilled water which was then added to 500 ml of acetonitrile. This gave an overall concentration of tetrabutyl ammonium phosphate of 0.01M in the mobile phase.

Chromatographic Apparatus

The liquid chromatograph consisted of a Waters 6000A constant-flow, reciprocating diaphragm pump, a stopped-flow injection system and a Cecil Instruments CE 2012 ultra-violet detector operated at 230 nm. Partisil 10-PAC (10 µm average size, Whatman Lab. Sales, Kent, Great Britain) was packed into a stainless-steel column (250 x 4.5 mm I.D.) by a high pressure slurry technique [5]. The mobile phase was pumped at ambient

Table 1

Recovery of Trimellitic Anhydride from GF/A Filters

Amount (µg)	Recovery[a] (%)	Coefficient of variation (%)
1.3	91.0	6.5
3.2	93.3	6.0
6.4	94.6	5.5
16.0	86.6	5.5

[a] mean of 6 determinations

temperature through the column at a flow-rate of 2 ml/min. Degassing of the eluent was performed immediately before use.

Preparation of Standard Trimellitic Anhydride Solution

0.2 g of trimellitic anhydride was accurately weighed into a 100 ml graduated flask and made to volume with 1M sodium hydroxide solution. On addition of the sodium hydroxide solution the anhydride is converted to the sodium salt of the corresponding acid. Suitable aliquots of this solution were diluted with 1M sodium hydroxide to give a series of standard solutions equivalent to 0.2 µg/ml – 4 µg/ml of TMA.

Determination of Desorption Efficiencies

The efficiency with which trimellitic anhydride was extracted from the glass fibre filters was determined by spiking the filters with 10 µl of a standard solution of TMA in diethyl ether over the range 1 µg - 20 µg. The loaded filters were placed in sample vials, sealed and left overnight. The filters were subsequently desorbed with 2 ml of 1M sodium hydroxide solution. Standards were prepared by injecting 10 µl of each of the solutions used for spiking into 2 ml of 1M sodium hydroxide. The filter desorbates, along with the appropriate standard solutions, were analysed and the desorption efficiency of trimellitic anhydride from the filters determined.

Method of Sampling and Analysis

A suitable volume of air (~ 100 l) is drawn through a GF/A filter contained in a Gelman filter holder (Gelman-Hawkesley, Nottingham Great Britain) at a flow-rate of 2 l/min. After sampling, the filter is placed in a sample vial fitted with a PTFE screw cap and 2 ml of 1M sodium hydroxide solution is added. Any trimellitic anhydride collected on the filter during air sampling is converted to the sodium salt of the corresponding acid. 10 µl of this solution is then injected into the liquid chromatograph. The peak height obtained is compared to those obtained from a series of 10 µl injections from the standard solutions.

Results and Discussion

It was not possible to analyse trimellitic anhydride directly on a reverse-phase chromatographic system due to its slow hydrolysis to trimellitic acid in the aqueous mobile phase. Good results however were obtained if the trimellitic anhydride was completely hydrolysed with 1M sodium hydroxide solution prior to analysis and an ion-pair chromatographic system used. In this case the retention time for the trimellitic acid peak was found to depend

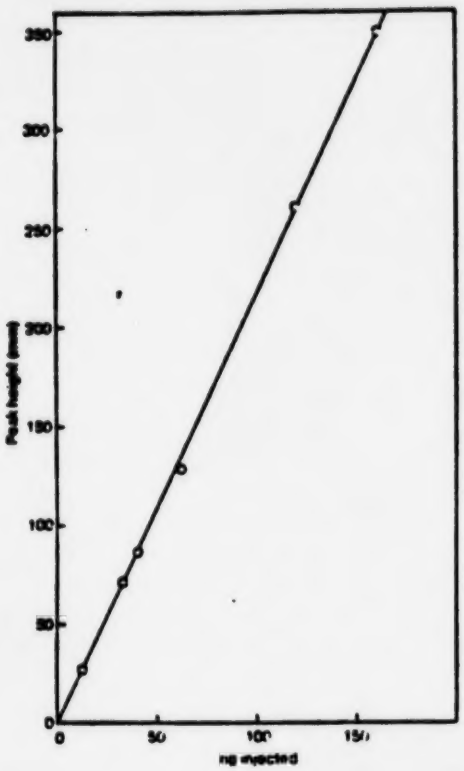

Figure 2

Calibration graph for TMA.

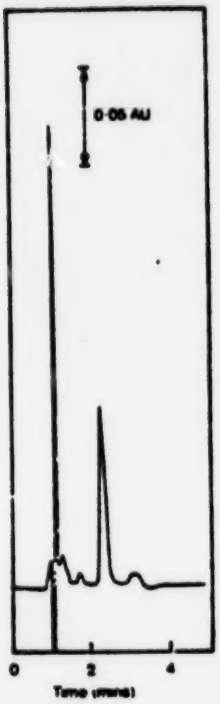

Figure 3

Chromatogram of a GF/A filter extract after sampling an 8 m³ air volume containing TMA at a concentration equivalent to 40 µg m⁻³. UV detector: 230 nm. Injection: 5 µl. Conditions as in text.

primarily on the ion-pair concentration. An increase in PIC-A concentration tended to shorten the retention time of the trimellitic acid peak whereas a change in the acetonitrile concentration had very little effect on retention time. The optimum conditions were found to be acetonitrile-tetrabutylammonium phosphate (0.02M) (50:50) on a Partisil 10-PAC column used at a flow rate of 2 ml/min. Good peak shape was obtained under these conditions with a retention time for the organic ion of 3 minutes. A typical chromatogram is shown in Fig. 1(a).

A calibration graph (Fig. 2) was prepared over the range 10 ng-160 ng injected and was found to be linear. The limit of detection based on a 10 mm peak height was 5 ng injected.

The results of the recovery experiments are shown in Table 1. The mean recovery from 24 spiked filters over the range 1.3 µg-16 µg of TMA loaded onto the filters was 91.4% (coefficient of variation, 5.8%).

Interferences from compounds such as phthalic anhydride and epoxy resins were not apparent. Fig. 1 (b) shows a chromatogram of a 1M sodium hydroxide solution extract from a filter spiked with both phthalic and trimellitic anhydride; as can be seen these respective organic ions are well separated from one another.

One limitation of the method is that it will not distinguish between trimellitic acid and trimellitic anhydride. Possible conversion of trimellitic anhydride to the corresponding acid by water vapour in ambient air may occur prior to the TMA actually being sampled onto a filter. However since TMA reacts relatively slowly with moisture in air to form the acid this was not felt to be a significant problem with regard to the interpretation of exposure levels for occupational hygiene work.

The method has been successfully used to measure TMA concentrations in air at a number of factories where TMA-based systems were in use. Fig. 3 shows a chromatogram of a filter extract from an air sample containing TMA obtained during one such factory visit. The method is fast and quantitative and will allow trimellitic anhydride to be measured at levels significantly lower than 40 µg/m³ in factory atmospheres.

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MS received 23 June 1980

APPENDIX VI

Worker exposure to particulates of TMA may be measured by using a Millipore Type AA membrane filter with a personal sampling pump, -uch as the MSA Model G, at a calibrated flow-rate of 2 liters per minute for a duration of one hour.

The sample can be analyzed by the attached method.

STANDARD OIL COMPANY (Indiana)
Research Department
Naperville, Illinois

LIQUID CHROMATOGRAPHIC ANALYSIS OF TRIMELLITIC ANHYDRIDE - PARTICULATES IN AIR

Summary

This method was developed to analyze particulate air for trimellitic anhydride (TMA) content. A measured volume of air is drawn through an appropriate filter device allowing particulates to be trapped on a removable filter element. This element is extracted with an acetonitrile/water mixture which effectively removes TMA and converts it to the analyzed species, trimellitic acid (TMLA).

Reagents and Apparatus

- Water - Distilled water treated with a Millipore Corporation Milli-Q water purification system.
- Phosphoric Acid - Matheson, Coleman, and Bell Reagent grade.
- Acetonitrile - Burdick and Jackson distilled in glass UV grade.
- Liquid Chromatographic Pump - Perkin-Elmer Series II
- Liquid Chromatographic Column - DuPont Instruments Zorbax ODS Reverse Phase, 15cm x 4.6mm i.d.
- Liquid Chromatographic Detector - Altex Model 151 UV absorbance detector.
- Injector Valve - Rheodyne Model 70-10.
- Mechanical Shaker - Burrell "Wrist-Action" Shaker.

Liquid Chromatographic Conditions

- Column Temperature - ambient
- Mobile Phase - 6.0% (vol/vol) acetonitrile and 0.1% (vol/vol) phosphoric acid in water
- Flow rate - 2.0 ml/min.
- Column Back Pressure - 1000 PSI, Nominal
- Detector Wavelength - 254 um
- Injector Loop Volume - 200µl

Procedure

The procedure as detailed here pertains only to workup and analysis of samples. Field sampling procedures are beyond the scope of this method.

A filter element (usually Millipore filter paper) containing particulates from sampled air is placed in a vial to which is added 10.0ml of chromatographic mobile phase. This vial is placed in a mechanical shaker and allowed to extract for 60 minutes. At the conclusion of this extraction period, the solution is decanted into a clean vial and stored until analysis can be performed.

A 200 µl aliquot of the extract solution is injected directly into the chromatographic column. A typical chromatogram for an actual sample containing approximately 5 µg of TMA is shown in Figure 1. Using conditions specified in this method, the retention volume of TMLA is 10.0ml (retention time of 5.0 minutes). Total analysis time will be dictated by other UV absorbing materials which may be present in the particulate sample. This will have to be determined on an individual basis. Furthermore, certain lots of filter paper contain extractable UV absorbing species which elute at approximately

120ml retention volume. When present these species contribute significantly to total analysis time.

Standard solutions are prepared with known amounts of TMLA which is preferred over TMA since TMA reacts with moisture in air. Calibration factors are determined from chromatographic peak heights resulting from these standard solutions. Since all calculations are based on external standardization, no weighing of samples or internal standards is required. The weight of TMA present in a sample is calculated by the following relationships:

$$\text{wt. TMA in sample} = \frac{(\text{analyzed amount TMLA in sample})(0.914)}{\text{\% recovery as a decimal fraction}}$$

where 0.914 is the ratio of molecular weights and is the factor for converting from TMLA to TMA

$$\text{Analyzed amount TMLA in sample} = \frac{\text{PkHt TMLA in sample}}{\text{PkHt TMLA in standard}} \text{ (wt. TMLA in standard)}$$

Precision and Recovery

Precision and recovery of the method were determined by analyzing four samples containing known amounts of TMA. These samples were prepared by adding known volumes of a standard ether solution of TMA directly to a Millipore filter paper. Analytical data for precision and recovery experiments are summarized in Table I.

Table I

Sample Number	Added TMA, µg	Analyzed TMA, µg	Recovery
J-33	5.1	4.4[1]	86.3%
J-34	5.1	4.4[2]	86.3%
J-35	20.4	18.2[1]	89.2%
J-36	20.4	17.6[1]	86.3%

1 - Average of two determinations.

2 - Average of five determinations with relative standard deviation of ± 2.9%.

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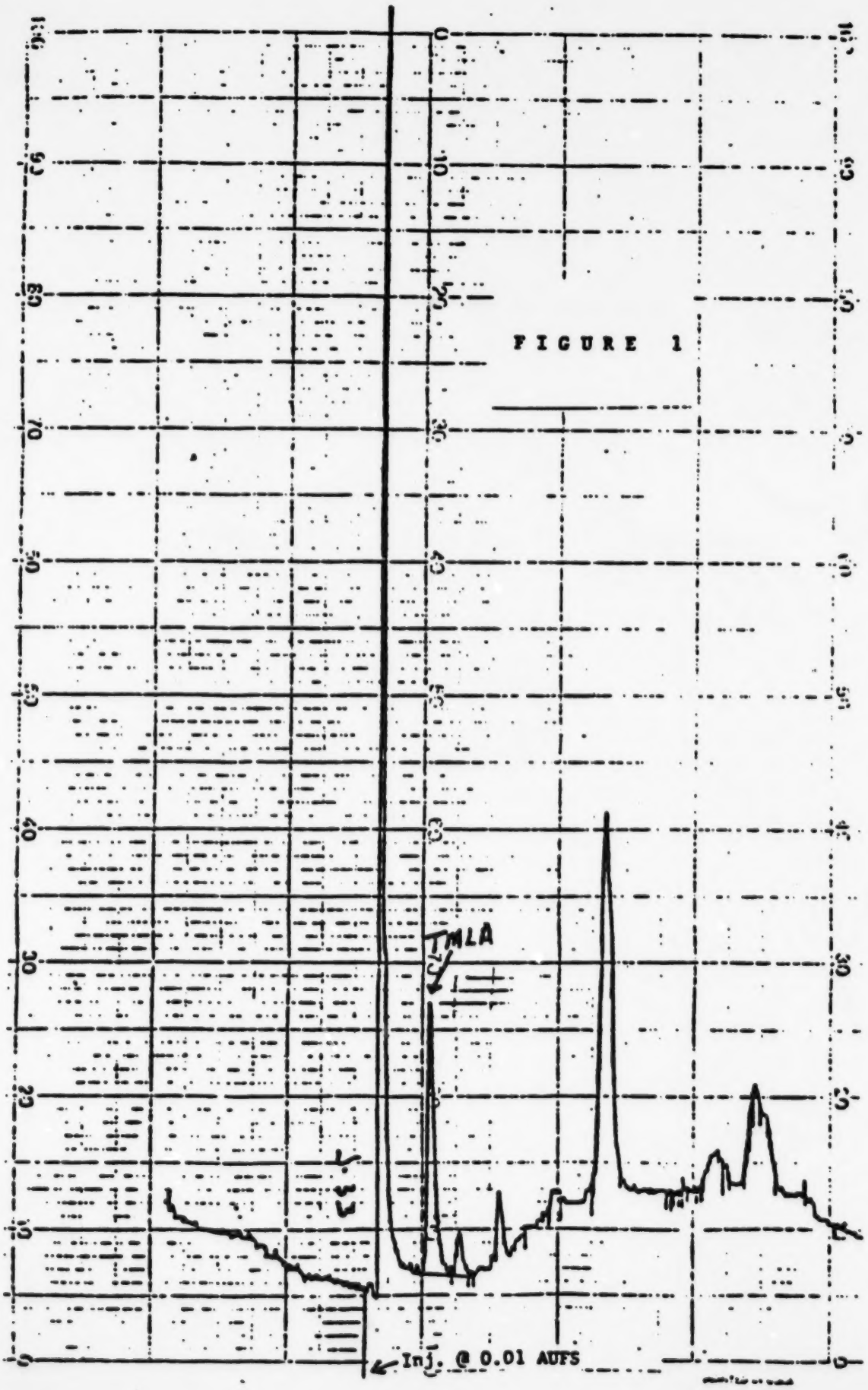

FIGURE 1

APPENDIX VII

Trimellitic anhydride–induced airway syndromes: Clinical and immunologic studies

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Clinical evaluation

The workers were assessed by standard techniques of history, physical examination when indicated, and skin tests. An outline of the major areas covered in the initial

TABLE I. Initial clinical evaluation form

I. Occupation
  A. Duties
  B. Nature of exposure to TMA
    1. Duration (current)
      Hours/day
      Days/week
    2. Type of exposure (location in TMA unit/handling)
    3. Nature of precautionary measures
    4. Adherence to these measures
    5. Duration of exposure (months or years)
II. Symptoms: Describe
  A. Ocular
  B. Nasal
  C. Chest
  D. Skin
  E. Other
III. Onset of symptoms in relation to exposure
  A. Immediate (minutes, hours)
  B. In relation to duration of occupational exposure (time after initial work exposure to TMA)
IV. Severity of symptoms
  A. Conscious of exposure (mild irritation)
  B. Significant acute or chronic symptoms in terms of discomfort or disability
  C. Hospitalization, work loss
V. Duration of symptoms (after exposure ended)
  A. Persistence (overnight, weekends)
VI. Previous work experience (occupational exposure)
VII. History of related or unrelated symptoms (current or remote)
  A. Rhinitis
  B. Asthma
  C. Eczema
  D. Smoking history (cough and sputum production)
  E. Animal exposure
VIII. Comments and opinions of exposed subjects

clinical evaluation is shown in Table I. Prick tests were done to inhalant allergens common to this geographic area, to a TMA human serum albumin conjugate (TMA-HSA), 3.4 mg/ml, to a sodium salt of TMA (1:200), and to TMA in acetone. Prick tests were read at 20 minutes and graded as in standard allergy practice. Patch testing was done to TMA in acetone (0.5 mg/ml) and read at 30 minutes. Subjects were asked to report reactions of late onset to the plant nurse.

Periodic chest x-rays had been taken on all the workers who were studied. These chest x-ray reports were reviewed.

Immunologic methods

Preparation of TMA human serum albumin conjugate (TMA-HSA). Fifty mg HSA (Pentex) was dissolved in 10 ml 9% $NaHCO_3$ and chilled in ice water at 0° C. Fifty mg TMA was slowly added with stirring and the mixture was allowed to react at 0° C for 60 minutes. The mixture was dialyzed against four changes of distilled water adjusted to pH 7.4 or until the dialysate at equilibrium had an optical density at

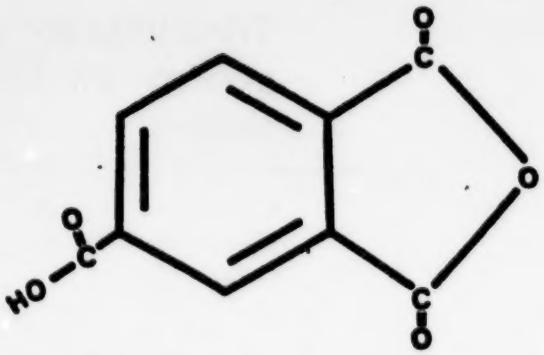

FIG. 1. The chemical structure of trimellitic anhydride (TMA).

240 nm (1 cm light path) of 0.05 or less. Sufficient Tris saline pH 7.6 was added to make the preparation isotonic. For prick testing, aliquots were sterilized by filtration through a 0.2 μ plain membrane (Nalge).

The molecular ratio of TMA to HSA was determined in the following manner. Absorption curves of solutions of HSA, the sodium salt of hydrolyzed TMA (NaTMA) and TMA-HSA, were prepared from 210 to 350 nm. HSA showed its highest optical density (O.D.) at 210 nm, which dropped to a minimum at 260 nm and then peaked at 280 nm. The O.D. of the TMA salt was highest at 210 nm, dropped rapidly until 230 nm, where a shoulder developed and dropped rapidly again starting at 250 nm. It appeared that a specific absorption peak was located in the vicinity of 240 nm. The O.D. pattern of the TMA-HSA conjugate combined the characteristics of both of the previous curves with a shoulder at 230 to 250 nm and a peak at 280 nm.

The molar concentrations of trimellityl groups in TMA conjugates were determined spectrophotometrically assuming that its molar extinction coefficient was the same in either the conjugated or the unconjugated form. This is the basis for determining many covalently bound ligands, including the widely used dinitrophenyl-protein conjugates. In the case of TMA, however, there is a small contribution of TMA to the absorbance of the HSA at 280 nm, and HSA contributes significantly to the absorbance of TMA at 240 nm. To compensate for these reciprocal contributions, the following procedure was employed. Solutions of HSA were prepared and the absorbance was read both at 280 nm (A_{280}) and 240 nm (A_{240}). It was established that the ratio $A_{280}:A_{240}$ was 1.65. Similarly for NaTMA solutions it was determined that $A_{280}:A_{240} = 0.125$. These calculations were performed:

Let T = A_{240} due to TMA
H = A_{240} due to HSA
E = observed A_{280} of TMA-HSA
F = observed A_{240} of TMA-HSA

Then at 280 nm $E = 1.00H + 0.125\,T$

$F = 1.65H + 1.000\,T$

Solving these simultaneous equations,

$$T = \frac{F - 1.65\,E}{0.794}$$

and as shown above $H = E - 0.125\,T$.

The molar concentrations of TMA and HSA and their ratio can then be calculated from their respective molar extinction coefficients. For four separate preparations the molecular ratio of TMA to HSA was calculated to range from 22 to 29. This preparation produced no immediate skin reactions in 5 nonexposed controls.

The TMA-HSA conjugate for immunologic testing was prepared at 0° C. which would restrict the reaction of TMA primarily to the epsilon amino groups of lysine. At 37° C. a more widespread and rapid reaction is possible.

Quantitation of IgG and IgE antibody against TMA-HSA

A polystyrene tube radioimmunoassay (PTRIA)[1] was used to detect antibodies of the IgG and IgE class against TMA-HSA. Briefly, the following reagents were added sequentially to polystyrene tubes with incubation periods and washes between additions: TMA-HSA, 1% HSA (to saturate any unfilled polystyrene surface binding sites), dilution of patient or control serum, heavy chain specific anti-IgG or anti-IgE, and finally ^{125}I-labeled IgG or IgE. The results are expressed as cpm ^{125}I IgG or ^{125}I IgE bound by the last layer. The cpm bound by a control serum pool, from three nonallergic individuals never exposed to TMA in industry, were then subtracted.

Inhibition of the reaction of ^{125}I TMA-HSA and IgE antibody by the sodium salt of TMA

IgE antibody to ^{125}I TMA-HSA was also measured by a method previously described.[2] Myeloma IgE adsorbed to the wall of a polystyrene tube and reacted with excess rabbit anti-IgE acts as an immunosorbent for the patient's IgE. TMA-HSA labeled with ^{125}I then reacted quantitatively with the IgE antibody on the solid phase. Several workers bound significant amounts of this labeled antigen. To demonstrate TMA hapten specificity of the IgE antibody, the unlabeled sodium salt of TMA (NaTMA), 5 mg/ml, was added with the ^{125}I TMA-HSA. ^{125}I TMA-HSA bound by the patient's IgE was determined in the presence and the absence of TMA salt and the percent inhibition of the NaTMA was calculated.

Radioiodination

TMA-HSA (100 μg) was labeled with ^{125}I using chloramine-T[3] according to the method described by Gleich.[4] The labeled TMA-HSA was 95% precipitable in 10% trichloroacetic acid and had a specific activity of 8,400 cpm per nanogram.

Immunoglobulin analysis

Serum IgG, IgA, and IgM concentrations were measured by radial immunodiffusion plates (Meloy Laboratories, Springfield, Va.). Serum IgE concentrations were determined by the double-antibody radioimmunoassay technique.[4]

Lymphocyte proliferation

Lymphoproliferation studies in response to TMA-HSA were performed by the whole blood technique of Pauly, Sokal, and Han[5] as previously described.[6] The final culture concentrations of TMA-HSA used were 17.0 mg/ml, 8.5 mg/ml, 0.85 mg/ml, and 0.085 mg/ml. Culture tubes were set up in triplicate. Stimulation indices of tritiated thymidine incorporation were calculated by dividing the mean cpm of the three stimulated cultures by the mean cpm of three unstimulated control cultures. A stimulation index of greater than two was considered significant.

Passive transfer of immediate-type hypersensitivity to TMA-HSA to a rhesus monkey

One-tenth milliliter of serum from worker 1 in serial 2-fold dilutions with appropriate control serum dilutions was injected intracutaneously. Forty-eight hours later the monkey received 4 ml of 0.5% Evans blue dye intravenously, followed in 15 minutes by intracutaneous injection of 0.05 ml of TMA-HSA (3.4 mg/ml) at the injected sites. The sites were examined in 30 min for bluing and edema.[7]

Histamine release from leukocytes in response to TMA-HSA

In three workers histamine release from peripheral blood leukocytes in response to TMA-HSA was performed by methods described previously.[8] Briefly, aliquots of cells in buffer were challenged with 0, 2, and 20 ng of TMA-HSA per milliliter of cells. After a 30-min incubation period the cell and supernate histamine were assayed and the percent histamine release calculated.

Rheumatoid factor analysis

Serum from all workers was analyzed for the presence of rheumatoid factor by the latex fixation method[9] and the titer determined by serial dilution.